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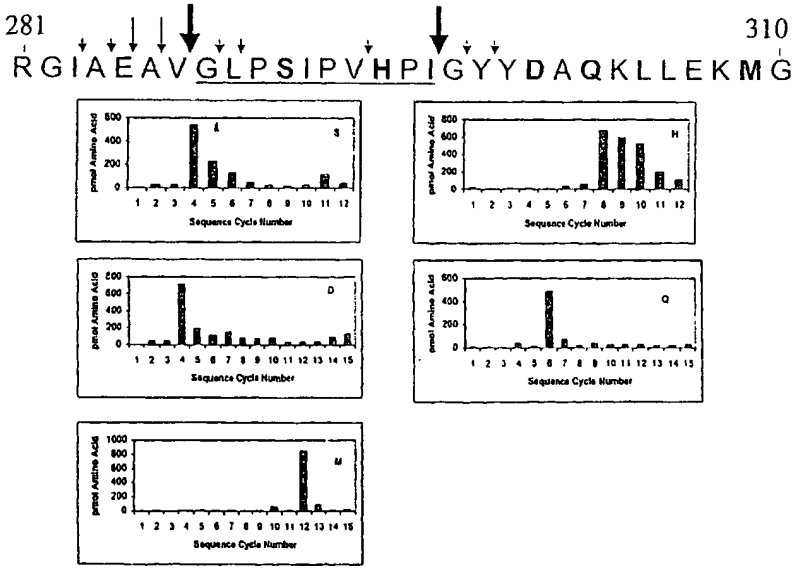

Pool sequencing of PSMA_281-310 digested for 60 min by Proteasome

(57) Abstract: Disclosed herein are polypeptides, including epitopes, clusters, and antigens. Also disclosed are compositions that include said polypeptides and methods for their use.

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EPITOPE SEQUENCES

Background of the Invention

Field of the Invention

The present invention generally relates to peptides, and nucleic acids encoding peptides, that are useful epitopes of target-associated antigens. More specifically, the invention relates to epitopes that have a high affinity for MHC class I and that are produced by target-specific proteasomes.

Description of the Related Art

Neoplasia and the Immune System

The neoplastic disease state commonly known as cancer is thought to result generally from a single cell growing out of control. The uncontrolled growth state typically results from a multi-step process in which a series of cellular systems fail, resulting in the genesis of a neoplastic cell. The resulting neoplastic cell rapidly reproduces itself, forms one or more tumors, and eventually may cause the death of the host.

Because the progenitor of the neoplastic cell shares the host's genetic material, neoplastic cells are largely unassailed by the host's immune system. During immune surveillance, the process in which the host's immune system surveys and localizes foreign materials, a neoplastic cell will appear to the host's immune surveillance machinery as a "self" cell.

Viruses and the Immune System

In contrast to cancer cells, virus infection involves the expression of clearly non-self antigens. As a result, many virus infections are successfully dealt with by the immune system with minimal clinical sequela. Moréover, it has been possible to develop effective vaccines for many of those infections that do cause serious disease. A variety of vaccine approaches have been used successfully to combat various diseases. These approaches include subunit vaccines consisting of individual proteins produced through recombinant DNA technology. Notwithstanding these advances, the selection and effective administration of minimal epitopes for use as viral vaccines has remained problematic.

In addition to the difficulties involved in epitope selection stands the problem of viruses that have evolved the capability of evading a host's immune system. Many viruses, especially viruses that establish persistent infections, such as members of the herpes and pox virus families, produce immunomodulatory molecules that permit the virus to evade the host's immune system. The effects of these immunomodulatory molecules on antigen presentation may be overcome by the targeting of select epitopes for administration as immunogenic compositions. To better understand the interaction of neoplastic cells and virally infected cells with the host's immune system, a discussion of the system's components follows below.

The immune system functions to discriminate molecules endogenous to an organism ("self" molecules) from material exogenous or foreign to the organism ("non-self" molecules). The immune system has two types of adaptive responses to foreign bodies based on the components that mediate the response: a humoral response and a cell-mediated response. The humoral response is mediated by antibodies, while the cell-mediated response involves cells classified as lymphocytes. Recent anticancer and antiviral strategies have focused on mobilizing the host immune system as a means of anticancer or antiviral treatment or therapy.

The immune system functions in three phases to protect the host from foreign bodies: the cognitive phase, the activation phase, and the effector phase. In the cognitive phase, the immune system recognizes and signals the presence of a foreign antigen or invader in the body. The foreign antigen can be, for example, a cell surface marker from a neoplastic cell or a viral protein. Once the system is aware of an invading body, antigen specific cells of the immune system proliferate and differentiate in response to the invader-triggered signals. The last stage is the effector stage in which the effector cells of the immune system respond to and neutralize the detected invader.

An array of effector cells implements an immune response to an invader. One type of effector cell, the B cell, generates antibodies targeted against foreign antigens encountered by the host. In combination with the complement system, antibodies direct the destruction of cells or organisms bearing the targeted antigen. Another type of effector cell is the natural killer cell (NK cell), a type of lymphocyte having the capacity to spontaneously recognize and destroy a variety of virus infected cells as well as malignant cell types. The method used by NK cells to recognize target cells is poorly understood.

Another type of effector cell, the T cell, has members classified into three subcategories, each playing a different role in the immune response. Helper T cells secrete cytokines which stimulate the proliferation of other cells necessary for mounting an effective immune response, while suppressor T cells down-regulate the immune response. A third category of T cell, the cytotoxic T cell (CTL), is capable of directly lysing a targeted cell presenting a foreign antigen on its surface.

The Major Histocompatibility Complex and T Cell Target Recognition

T cells are antigen-specific immune cells that function in response to specific antigen signals. B lymphocytes and the antibodies they produce are also antigen-specific entities. However, unlike B lymphocytes, T cells do not respond to antigens in a free or soluble form. For a T cell to respond to an antigen, it requires the antigen to be processed to peptides which are then bound to a presenting structure encoded in the major histocompatibility complex (MHC). This requirement is called "MHC restriction" and it is the mechanism by which T cells differentiate "self" from "non-self" cells. If an antigen is not displayed by a recognizable MHC molecule, the T cell will not recognize and act on the antigen signal. T cells specific for a peptide bound to a recognizable MHC

molecule bind to these MHC-peptide complexes and proceed to the next stages of the immune response.

There are two types of MHC, class I MHC and class II MHC. T Helper cells ($CD4^+$) predominately interact with class II MHC proteins while cytolytic T cells ($CD8^+$) predominately interact with class I MHC proteins. Both classes of MHC protein are transmembrane proteins with a majority of their structure on the external surface of the cell. Additionally, both classes of MHC proteins have a peptide binding cleft on their external portions. It is in this cleft that small fragments of proteins, endogenous or foreign, are bound and presented to the extracellular environment.

Cells called "professional antigen presenting cells" (pAPCs) display antigens to T cells using the MHC proteins but additionally express various co-stimulatory molecules depending on the particular state of differentiation/activation of the pAPC. When T cells, specific for the peptide bound to a recognizable MHC protein, bind to these MHC-peptide complexes on pAPCs, the specific co-stimulatory molecules that act upon the T cell direct the path of differentiation/activation taken by the T cell. That is, the co-stimulation molecules affect how the T cell will act on antigenic signals in future encounters as it proceeds to the next stages of the immune response.

As discussed above, neoplastic cells are largely ignored by the immune system. A great deal of effort is now being expended in an attempt to harness a host's immune system to aid in combating the presence of neoplastic cells in a host. One such area of research involves the formulation of anticancer vaccines.

Anticancer Vaccines

Among the various weapons available to an oncologist in the battle against cancer is the immune system of the patient. Work has been done in various attempts to cause the immune system to combat cancer or neoplastic diseases. Unfortunately, the results to date have been largely disappointing. One area of particular interest involves the generation and use of anticancer vaccines.

To generate a vaccine or other immunogenic composition, it is necessary to introduce to a subject an antigen or epitope against which an immune response may be mounted. Although neoplastic cells are derived from and therefore are substantially identical to normal cells on a genetic level, many neoplastic cells are known to present tumor-associated antigens (TuAAs). In theory, these antigens could be used by a subject's immune system to recognize these antigens and attack the neoplastic cells. In reality, however, neoplastic cells generally appear to be ignored by the host's immune system.

A number of different strategies have been developed in an attempt to generate vaccines with activity against neoplastic cells. These strategies include the use of tumor-associated antigens as immunogens. For example, U.S. Patent No. 5,993,828, describes a method for producing an

immune response against a particular subunit of the Urinary Tumor Associated Antigen by administering to a subject an effective dose of a composition comprising inactivated tumor cells having the Urinary Tumor Associated Antigen on the cell surface and at least one tumor associated antigen selected from the group consisting of GM-2, GD-2, Fetal Antigen and Melanoma Associated Antigen. Accordingly, this patent describes using whole, inactivated tumor cells as the immunogen in an anticancer vaccine.

Another strategy used with anticancer vaccines involves administering a composition containing isolated tumor antigens. In one approach, MAGE-A1 antigenic peptides were used as an immunogen. (See Chaux, P., *et al.*, "Identification of Five MAGE-A1 Epitopes Recognized by Cytolytic T Lymphocytes Obtained by *In Vitro* Stimulation with Dendritic Cells Transduced with MAGE-A1," J. Immunol., 163(5):2928-2936 (1999)). There have been several therapeutic trials using MAGE-A1 peptides for vaccination, although the effectiveness of the vaccination regimes was limited. The results of some of these trials are discussed in Vose, J.M., "Tumor Antigens Recognized by T Lymphocytes," 10th European Cancer Conference, Day 2, Sept. 14, 1999.

In another example of tumor associated antigens used as vaccines, Scheinberg, *et al.* treated 12 chronic myelogenous leukemia (CML) patients already receiving interferon (IFN) or hydroxyurea with 5 injections of class I-associated bcr-abl peptides with a helper peptide plus the adjuvant QS-21. Scheinberg, D.A., *et al.*, "BCR-ABL Breakpoint Derived Oncogene Fusion Peptide Vaccines Generate Specific Immune Responses in Patients with Chronic Myelogenous Leukemia (CML) [Abstract 1665], American Society of Clinical Oncology 35th Annual Meeting, Atlanta (1999). Proliferative and delayed type hypersensitivity (DTH) T cell responses indicative of T-helper activity were elicited, but no cytolytic killer T cell activity was observed within the fresh blood samples.

Additional examples of attempts to identify TuAAs for use as vaccines are seen in the recent work of Cebon, *et al.* and Scheibenbogen, *et al.* Cebon, *et al.* immunized patients with metastatic melanoma using intradermallly administered MART-1_{26-35} peptide with IL-12 in increasing doses given either subcutaneously or intravenously. Of the first 15 patients, 1 complete remission, 1 partial remission, and 1 mixed response were noted. Immune assays for T cell generation included DTH, which was seen in patients with or without IL-12. Positive CTL assays were seen in patients with evidence of clinical benefit, but not in patients without tumor regression. Cebon, *et al.*, "Phase I Studies of Immunization with Melan-A and IL-12 in HLA A2+ Positive Patients with Stage III and IV Malignant Melanoma," [Abstract 1671], American Society of Clinical Oncology 35th Annual Meeting, Atlanta (1999).

Scheibenbogen, *et al.* immunized 18 patients with 4 HLA class I restricted tyrosinase peptides, 16 with metastatic melanoma and 2 adjuvant patients. Scheibenbogen, *et al.*,

"Vaccination with Tyrosinase peptides and GM-CSF in Metastatic Melanoma: a Phase II Trial," [Abstract 1680], American Society of Clinical Oncology 35th Annual Meeting, Atlanta (1999). Increased CTL activity was observed in 4/15 patients, 2 adjuvant patients, and 2 patients with evidence of tumor regression. As in the trial by Cebon, *et al.*, patients with progressive disease did not show boosted immunity. In spite of the various efforts expended to date to generate efficacious anticancer vaccines, no such composition has yet been developed.

Antiviral Vaccines

Vaccine strategies to protect against viral diseases have had many successes. Perhaps the most notable of these is the progress that has been made against the disease small pox, which has been driven to extinction. The success of the polio vaccine is of a similar magnitude.

Viral vaccines can be grouped into three classifications: live attenuated virus vaccines, such as vaccinia for small pox, the Sabin poliovirus vaccine, and measles mumps and rubella; whole killed or inactivated virus vaccines, such as the Salk poliovirus vaccine, hepatitis A virus vaccine and the typical influenza virus vaccines; and subunit vaccines, such as hepatitis B. Due to their lack of a complete viral genome, subunit vaccines offer a greater degree of safety than those based on whole viruses.

The paradigm of a successful subunit vaccine is the recombinant hepatitis B vaccine based on the viruses envelope protein. Despite much academic interest in pushing the reductionist subunit concept beyond single proteins to individual epitopes, the efforts have yet to bear much fruit. Viral vaccine research has also concentrated on the induction of an antibody response although cellular responses also occur. However, many of the subunit formulations are particularly poor at generating a CTL response.

Summary of the Invention

Previous methods of priming professional antigen presenting cells (pAPCs) to display target cell epitopes have relied simply on causing the pAPCs to express target-associated antigens (TAAs), or epitopes of those antigens which are thought to have a high affinity for MHC I molecules. However, the proteasomal processing of such antigens results in presentation of epitopes on the pAPC that do not correspond to the epitopes present on the target cells.

Using the knowledge that an effective cellular immune response requires that pAPCs present the same epitope that is presented by the target cells, the present invention provides epitopes that have a high affinity for MHC I, and that correspond to the processing specificity of the housekeeping proteasome, which is active in peripheral cells. These epitopes thus correspond to those presented on target cells. The use of such epitopes in vaccines can activate the cellular immune response to recognize the correctly processed TAA and can result in removal of target cells that present such epitopes. In some embodiments, the housekeeping epitopes provided herein

can be used in combination with immune epitopes, generating a cellular immune response that is competent to attack target cells both before and after interferon induction. In other embodiments the epitopes are useful in the diagnosis and monitoring of the target-associated disease and in the generation of immunological reagents for such purposes.

Embodiments of the invention relate to isolated epitopes, and antigens or polypeptides that comprise the epitopes. Preferred embodiments include an epitope or antigen having the sequence as disclosed in Table 1. Other embodiments can include an epitope cluster comprising a polypeptide from Table 1. Further, embodiments include a polypeptide having substantial similarity to the already mentioned epitopes, polypeptides, antigens, or clusters. Other preferred embodiments include a polypeptide having functional similarity to any of the above. Still further embodiments relate to a nucleic acid encoding the polypeptide of any of the epitopes, clusters, antigens, and polypeptides from Table 1 and mentioned herein. For purposes of the following summary, discussions of other embodiments of the invention, when making reference to "the epitope," or "the epitopes" may refer without limitation to all of the foregoing forms of the epitope.

The epitope can be immunologically active. The polypeptide comprising the epitope can be less than about 30 amino acids in length, more preferably, the polypeptide is 8 to 10 amino acids in length, for example. Substantial or functional similarity can include addition of at least one amino acid, for example, and the at least one additional amino acid can be at an N-terminus of the polypeptide. The substantial or functional similarity can include a substitution of at least one amino acid.

The epitope, cluster, or polypeptide comprising the same can have affinity to an HLA-A2 molecule. The affinity can be determined by an assay of binding, by an assay of restriction of epitope recognition, by a prediction algorithm, and the like. The epitope, cluster, or polypeptide comprising the same can have affinity to an HLA-B7, HLA-B51 molecule, and the like.

In preferred embodiments the polypeptide can be a housekeeping epitope. The epitope or polypeptide can correspond to an epitope displayed on a tumor cell, to an epitope displayed on a neovasculature cell, and the like. The epitope or polypeptide can be an immune epitope. The epitope, cluster and/or polypeptide can be a nucleic acid.

Other embodiments relate to pharmaceutical compositions comprising the polypeptides, including an epitope from Table 1, a cluster, or a polypeptide comprising the same, and a pharmaceutically acceptable adjuvant, carrier, diluent, excipient, and the like. The adjuvant can be a polynucleotide. The polynucleotide can include a dinucleotide, which can be CpG, for example. The adjuvant can be encoded by a polynucleotide. The adjuvant can be a cytokine and the cytokine can be, for example, GM-CSF.

The pharmaceutical compositions can further include a professional antigen-presenting cell (pAPC). The pAPC can be a dendritic cell, for example. The pharmaceutical composition can further include a second epitope. The second epitope can be a polypeptide, a nucleic acid, a housekeeping epitope, an immune epitope, and the like.

Still further embodiments relate to pharmaceutical compositions that include any of the nucleic acids discussed herein, including those that encode polypeptides that comprise epitopes or antigens from Table 1. Such compositions can include a pharmaceutically acceptable adjuvant, carrier, diluent, excipient, and the like.

Other embodiments relate to recombinant constructs that include such a nucleic acid as described herein, including those that encode polypeptides that comprise epitopes or antigens from Table 1. The constructs can further include a plasmid, a viral vector, an artificial chromosome, and the like. The construct can further include a sequence encoding at least one feature, such as for example, a second epitope, an IRES, an ISS, an NIS, a ubiquitin, and the like.

Further embodiments relate to purified antibodies that specifically bind to at least one of the epitopes in Table 1. Other embodiments relate to purified antibodies that specifically bind to a peptide-MHC protein complex comprising an epitope disclosed in Table 1 or any other suitable epitope. The antibody from any embodiment can be a monoclonal antibody or a polyclonal antibody.

Still other embodiments relate to multimeric MHC-peptide complexes that include an epitope, such as, for example, an epitope disclosed in Table 1. Also, contemplated are antibodies specific for the complexes.

Embodiments relate to isolated T cells expressing a T cell receptor specific for an MHC-peptide complex. The complex can include an epitope, such as, for example, an epitope disclosed in Table 1. The T cell can be produced by an *in vitro* immunization and can be isolated from an immunized animal. Embodiments relate to T cell clones, including cloned T cells, such as those discussed above. Embodiments also relate to polyclonal population of T cells. Such populations can include a T cell, as described above, for example.

Still further embodiments relate to pharmaceutical compositions that include a T cell, such as those described above, for example, and a pharmaceutically acceptable adjuvant, carrier, diluent, excipient, and the like.

Embodiments of the invention relate to isolated protein molecules comprising the binding domain of a T cell receptor specific for an MHC-peptide complex. The complex can include an epitope as disclosed in Table 1. The protein can be multivalent. Other embodiments relate to isolated nucleic acids encoding such proteins. Still further embodiments relate to recombinant constructs that include such nucleic acids.

Other embodiments of the invention relate to host cells expressing a recombinant construct as described herein, including constructs encoding an epitope, cluster or polypeptide comprising the same, disclosed in Table 1, for example. The host cell can be a dendritic cell, macrophage, tumor cell, tumor-derived cell, a bacterium, fungus, protozoan, and the like. Embodiments also relate to pharmaceutical compositions that include a host cell, such as those discussed herein, and a pharmaceutically acceptable adjuvant, carrier, diluent, excipient, and the like.

Still other embodiments relate to vaccines or immunotherapeutic compositions that include at least one component, such as, for example, an epitope disclosed in Table 1 or otherwise described herein; a cluster that includes such an epitope, an antigen or polypeptide that includes such an epitope; a composition as described above and herein; a construct as described above and herein, a T cell, or a host cell as described above and herein.

Further embodiments relate to methods of treating an animal. The methods can include administering to an animal a pharmaceutical composition, such as, a vaccine or immunotherapeutic composition, including those disclosed above and herein. The administering step can include a mode of delivery, such as, for example, transdermal, intranodal, perinodal, oral, intravenous, intradermal, intramuscular, intraperitoneal, mucosal, aerosol inhalation, instillation, and the like. The method can further include a step of assaying to determine a characteristic indicative of a state of a target cell or target cells. The method can include a first assaying step and a second assaying step, wherein the first assaying step precedes the administering step, and wherein the second assaying step follows the administering step. The method can further include a step of comparing the characteristic determined in the first assaying step with the characteristic determined in the second assaying step to obtain a result. The result can be for example, evidence of an immune response, a diminution in number of target cells, a loss of mass or size of a tumor comprising target cells, a decrease in number or concentration of an intracellular parasite infecting target cells, and the like.

Embodiments relate to methods of evaluating immunogenicity of a vaccine or immunotherapeutic composition. The methods can include administering to an animal a vaccine or immunotherapeutic, such as those described above and elsewhere herein, and evaluating immunogenicity based on a characteristic of the animal. The animal can be HLA-transgenic.

Other embodiments relate to methods of evaluating immunogenicity that include *in vitro* stimulation of a T cell with the vaccine or immunotherapeutic composition, such as those described above and elsewhere herein, and evaluating immunogenicity based on a characteristic of the T cell. The stimulation can be a primary stimulation.

Still further embodiments relate to methods of making a passive/adoptive immunotherapeutic. The methods can include combining a T cell or a host cell, such as those

described above and elsewhere herein, with a pharmaceutically acceptable adjuvant, carrier, diluent, excipient, and the like.

Other embodiments relate to methods of determining specific T cell frequency, and can include the step of contacting T cells with a MHC-peptide complex comprising an epitope disclosed in Table 1, or a complex comprising a cluster or antigen comprising such an epitope. The contacting step can include at least one feature, such as, for example, immunization, restimulation, detection, enumeration, and the like. The method can further include ELISPOT analysis, limiting dilution analysis, flow cytometry, in situ hybridization, the polymerase chain reaction, any combination thereof, and the like.

Embodiments relate to methods of evaluating immunologic response. The methods can include the above-described methods of determining specific T cell frequency carried out prior to and subsequent to an immunization step.

Other embodiments relate to methods of evaluating immunologic response. The methods can include determining frequency, cytokine production, or cytolytic activity of T cells, prior to and subsequent to a step of stimulation with MHC-peptide complexes comprising an epitope, such as, for example an epitope from Table 1, a cluster or a polypeptide comprising such an epitope.

Further embodiments relate to methods of diagnosing a disease. The methods can include contacting a subject tissue with at least one component, including, for example, a T cell, a host cell, an antibody, a protein, including those described above and elsewhere herein; and diagnosing the disease based on a characteristic of the tissue or of the component. The contacting step can take place *in vivo* or *in vitro*, for example.

Still other embodiments relate to methods of making a vaccine. The methods can include combining at least one component, an epitope, a composition, a construct, a T cell, a host cell; including any of those described above and elsewhere herein, with a pharmaceutically acceptable adjuvant, carrier, diluent, excipient, and the like.

Embodiments relate to computer readable media having recorded thereon the sequence of any one of SEQ ID NOS: 1 -602, in a machine having a hardware or software that calculates the physical, biochemical, immunologic, molecular genetic properties of a molecule embodying said sequence, and the like.

Still other embodiments relate to methods of treating an animal. The methods can include combining the method of treating an animal that includes administering to the animal a vaccine or immunotherapeutic composition, such as described above and elsewhere herein, combined with at least one mode of treatment, including, for example, radiation therapy, chemotherapy, biochemotherapy, surgery, and the like.

Further embodiments relate to isolated polypeptides that include an epitope cluster. In preferred embodiments the cluster can be from a target-associated antigen having the sequence as disclosed in any one of Tables 25-44, wherein the amino acid sequence includes not more than about 80% of the amino acid sequence of the antigen.

Other embodiments relate to vaccines or immunotherapeutic products that include an isolated peptide as described above and elsewhere herein. Still other embodiments relate to isolated polynucleotides encoding a polypeptide as described above and elsewhere herein. Other embodiments relate vaccines or immunotherapeutic products that include these polynucleotides. The polynucleotide can be DNA, RNA, and the like.

Still further embodiments relate to kits comprising a delivery device and any of the embodiments mentioned above and elsewhere herein. The delivery device can be a catheter, a syringe, an internal or external pump, a reservoir, an inhaler, microinjector, a patch, and any other like device suitable for any route of delivery. As mentioned, the kit, in addition to the delivery device also includes any of the embodiments disclosed herein. For example, without limitations, the kit can include an isolated epitope, a polypeptide, a cluster, a nucleic acid, an antigen, a pharmaceutical composition that includes any of the foregoing, an antibody, a T cell, a T cell receptor, an epitope-MHC complex, a vaccine, an immunotherapeutic, and the like. The kit can also include items such as detailed instructions for use and any other like item.

Brief Description of the Drawings

Figure 1 is a sequence alignment of NY-ESO-1 and several similar protein sequences.

Figure 2 graphically represents a plasmid vaccine backbone useful for delivering nucleic acid-encoded epitopes.

Figures 3A and 3B are FACS profiles showing results of HLA-A2 binding assays for tyrosinase$_{207-215}$ and tyrosinase$_{208-216}$.

Figure 3C shows cytolytic activity against a tyrosinase epitope by human CTL induced by *in vitro* immunization.

Figure 4 is a T=120 min. time point mass spectrum of the fragments produced by proteasomal cleavage of SSX-2$_{31-68}$.

Figure 5 shows a binding curve for HLA-A2:SSX-2$_{41-49}$ with controls.

Figure 6 shows specific lysis of SSX-2$_{41-49}$–pulsed targets by CTL from SSX–2$_{41-49}$–immunized HLA-A2 transgenic mice.

Figure 7A, B, and C show results of N-terminal pool sequencing of a T=60 min. time point aliquot of the PSMA$_{163-192}$ proteasomal digest.

Figure 8 shows binding curves for HLA-A2:PSMA$_{168-177}$ and HLA-A2:PSMA$_{288-297}$ with controls.

Figure 9 shows results of N-terminal pool sequencing of a T=60 min. time point aliquot of the $PSMA_{281-310}$ proteasomal digest.

Figure 10 shows binding curves for HLA-A2:$PSMA_{461-469}$, HLA-A2:$PSMA_{460-469}$, and HLA-A2:$PSMA_{663-671}$, with controls.

Figure 11 shows the results of a γ-IFN-based ELISPOT assay detecting $PSMA_{463-471}$-reactive HLA-$A1^+$ $CD8^+$ T cells.

Figure 12 shows blocking of reactivity of the T cells used in figure 10 by anti-HLA-A1 mAb, demonstrating HLA-A1-restricted recognition.

Figure 13 shows a binding curve for HLA-A2:$PSMA_{663-671}$, with controls.

Figure 14 shows a binding curve for HLA-A2:$PSMA_{662-671}$, with controls.

Figure 15. Comparison of anti-peptide CTL responses following immunization with various doses of DNA by different routes of injection.

Figure 16. Growth of transplanted gp33 expressing tumor in mice immunized by i.ln. injection of gp33 epitope-expressing, or control, plasmid.

Figure 17. Amount of plasmid DNA detected by real-time PCR in injected or draining lymph nodes at various times after i.ln. of i.m. injection, respectively.

Detailed Description of the Preferred Embodiment

Definitions

Unless otherwise clear from the context of the use of a term herein, the following listed terms shall generally have the indicated meanings for purposes of this description.

PROFESSIONAL ANTIGEN-PRESENTING CELL (pAPC) – a cell that possesses T cell costimulatory molecules and is able to induce a T cell response. Well characterized pAPCs include dendritic cells, B cells, and macrophages.

PERIPHERAL CELL – a cell that is not a pAPC.

HOUSEKEEPING PROTEASOME – a proteasome normally active in peripheral cells, and generally not present or not strongly active in pAPCs.

IMMUNE PROTEASOME – a proteasome normally active in pAPCs; the immune proteasome is also active in some peripheral cells in infected tissues.

EPITOPE – a molecule or substance capable of stimulating an immune response. In preferred embodiments, epitopes according to this definition include but are not necessarily limited to a polypeptide and a nucleic acid encoding a polypeptide, wherein the polypeptide is capable of stimulating an immune response. In other preferred embodiments, epitopes according to this definition include but are not necessarily limited to peptides presented on the surface of cells, the peptides being non-covalently bound to the binding cleft of class I MHC, such that they can interact with T cell receptors.

MHC EPITOPE – a polypeptide having a known or predicted binding affinity for a mammalian class I or class II major histocompatibility complex (MHC) molecule.

HOUSEKEEPING EPITOPE – In a preferred embodiment, a housekeeping epitope is defined as a polypeptide fragment that is an MHC epitope, and that is displayed on a cell in which housekeeping proteasomes are predominantly active. In another preferred embodiment, a housekeeping epitope is defined as a polypeptide containing a housekeeping epitope according to the foregoing definition, that is flanked by one to several additional amino acids. In another preferred embodiment, a housekeeping epitope is defined as a nucleic acid that encodes a housekeeping epitope according to the foregoing definitions.

IMMUNE EPITOPE – In a preferred embodiment, an immune epitope is defined as a polypeptide fragment that is an MHC epitope, and that is displayed on a cell in which immune proteasomes are predominantly active. In another preferred embodiment, an immune epitope is defined as a polypeptide containing an immune epitope according to the foregoing definition, that is flanked by one to several additional amino acids. In another preferred embodiment, an immune epitope is defined as a polypeptide including an epitope cluster sequence, having at least two polypeptide sequences having a known or predicted affinity for a class I MHC. In yet another preferred embodiment, an immune epitope is defined as a nucleic acid that encodes an immune epitope according to any of the foregoing definitions.

TARGET CELL – a cell to be targeted by the vaccines and methods of the invention. Examples of target cells according to this definition include but are not necessarily limited to: a neoplastic cell and a cell harboring an intracellular parasite, such as, for example, a virus, a bacterium, or a protozoan.

TARGET-ASSOCIATED ANTIGEN (TAA) – a protein or polypeptide present in a target cell.

TUMOR-ASSOCIATED ANTIGENS (TuAA) – a TAA, wherein the target cell is a neoplastic cell.

HLA EPITOPE – a polypeptide having a known or predicted binding affinity for a human class I or class II HLA complex molecule.

ANTIBODY – a natural immunoglobulin (Ig), poly- or monoclonal, or any molecule composed in whole or in part of an Ig binding domain, whether derived biochemically or by use of recombinant DNA. Examples include *inter alia*, F(ab), single chain Fv, and Ig variable region-phage coat protein fusions.

ENCODE – an open-ended term such that a nucleic acid encoding a particular amino acid sequence can consist of codons specifying that (poly)peptide, but can also comprise additional

sequences either translatable, or for the control of transcription, translation, or replication, or to facilitate manipulation of some host nucleic acid construct.

SUBSTANTIAL SIMILARITY – this term is used to refer to sequences that differ from a reference sequence in an inconsequential way as judged by examination of the sequence. Nucleic acid sequences encoding the same amino acid sequence are substantially similar despite differences in degenerate positions or modest differences in length or composition of any non-coding regions. Amino acid sequences differing only by conservative substitution or minor length variations are substantially similar. Additionally, amino acid sequences comprising housekeeping epitopes that differ in the number of N-terminal flanking residues, or immune epitopes and epitope clusters that differ in the number of flanking residues at either terminus, are substantially similar. Nucleic acids that encode substantially similar amino acid sequences are themselves also substantially similar.

FUNCTIONAL SIMILARITY – this term is used to refer to sequences that differ from a reference sequence in an inconsequential way as judged by examination of a biological or biochemical property, although the sequences may not be substantially similar. For example, two nucleic acids can be useful as hybridization probes for the same sequence but encode differing amino acid sequences. Two peptides that induce cross-reactive CTL responses are functionally similar even if they differ by non-conservative amino acid substitutions (and thus do not meet the substantial similarity definition). Pairs of antibodies, or TCRs, that recognize the same epitope can be functionally similar to each other despite whatever structural differences exist. In testing for functional similarity of immunogenicity one would generally immunize with the "altered" antigen and test the ability of the elicited response (Ab, CTL, cytokine production, etc.) to recognize the target antigen. Accordingly, two sequences may be designed to differ in certain respects while retaining the same function. Such designed sequence variants are among the embodiments of the present invention.

Table 1A. SEQ ID NOS.* including epitopes in Examples 1-7, 13.

SEQ ID NO	IDENTITY	SEQUENCE
1	Tyr 207-216	FLPWHRLFLL
2	Tyrosinase protein	Accession number**: P14679
3	SSX-2 protein	Accession number: NP_003138
4	PSMA protein	Accession number: NP_004467
5	Tyrosinase cDNA	Accession number: NM_000372
6	SSX-2 cDNA	Accession number: NM_003147
7	PSMA cDNA	Accession number: NM_004476
8	Tyr 207-215	FLPWHRLFL
9	Tyr 208-216	LPWHRLFLL

10	SSX-2 31-68	YFSKEEWEKMKASEKIFYVYMKRKYEAMTKLGFK ATLP
11	SSX-2 32-40	FSKEEWEKM
12	SSX-2 39-47	KMKASEKIF
13	SSX-2 40-48	MKASEKIFY
14	SSX-2 39-48	KMKASEKIFY
15	SSX-2 41-49	KASEKIFYV
16	SSX-2 40-49	MKASEKIFYV
17	SSX-2 41-50	KASEKIFYVY
18	SSX-2 42-49	ASEKIFYVY
19	SSX-2 53-61	RKYEAMTKL
20	SSX-2 52-61	KRKYEAMTKL
21	SSX-2 54-63	KYEAMTKLGF
22	SSX-2 55-63	YEAMTKLGF
23	SSX-2 56-63	EAMTKLGF
24	HBV18-27	FLPSDYFPSV
25	HLA-B44 binder	AEMGKYSFY
26	SSX-1 41-49	KYSEKISYV
27	SSX-3 41-49	KVSEKIVYV
28	SSX-4 41-49	KSSEKIVYV
29	SSX-5 41-49	KASEKIIYV
30	PSMA163-192	AFSPQGMPEGDLVYVNYARTEDFFKLERDM
31	PSMA 168-190	GMPEGDLVYVNYARTEDFFKLER
32	PSMA 169-177	MPEGDLVYV
33	PSMA 168-177	GMPEGDLVYV
34	PSMA 168-176	GMPEGDLVY
35	PSMA 167-176	QGMPEGDLVY
36	PSMA 169-176	MPEGDLVY
37	PSMA 171-179	EGDLVYVNY
38	PSMA 170-179	PEGDLVYVNY
39	PSMA 174-183	LVYVNYARTE
40	PSMA 177-185	VNYARTEDF
41	PSMA 176-185	YVNYARTEDF
42	PSMA 178-186	NYARTEDFF
43	PSMA 179-186	YARTEDFF
44	PSMA 181-189	RTEDFFKLE
45	PSMA 281-310	RGIAEAVGLPSIPVHPIGYYDAQKLLEKMG
46	PSMA 283-307	IAEAVGLPSIPVHPIGYYDAQKLLE
47	PSMA 289-297	LPSIPVHPI
48	PSMA 288-297	GLPSIPVHPI
49	PSMA 297-305	IGYYDAQKL
50	PSMA 296-305	PIGYYDAQKL

51	PSMA 291-299	SIPVHPIGY
52	PSMA 290-299	PSIPVHPIGY
53	PSMA 292-299	IPVHPIGY
54	PSMA 299-307	YYDAQKLLE
55	PSMA454-481	SSIEGNYTLRVDCTPLMYSLVHLTKEL
56	PSMA 456-464	IEGNYTLRV
57	PSMA 455-464	SIEGNYTLRV
58	PSMA 457-464	EGNYTLRV
59	PSMA 461-469	TLRVDCTPL
60	PSMA 460-469	YTLRVDCTPL
61	PSMA 462-470	LRVDCTPLM
62	PSMA 463-471	RVDCTPLMY
63	PSMA 462-471	LRVDCTPLMY
64	PSMA653-687	FDKSNPIVLRMMNDQLMFLERAFIDPLGLPDRPFY
65	PSMA 660-681	VLRMMNDQLMFLERAFIDPLGL
66	PSMA 663-671	MMNDQLMFL
67	PSMA 662-671	RMMNDQLMFL
68	PSMA 662-670	RMMNDQLMF
69	Tyr 1-17	MLLAVLYCLLWSFQTSA

Table 1B. SEQ ID NOS.* including epitopes in Examples 14 and 15.

SEQ ID NO	IDENTITY	SEQUENCE
70	GP100 protein²	**Accession number: P40967
71	MAGE-1 protein	Accession number: P43355
72	MAGE-2 protein	Accession number: P43356
73	MAGE-3 protein	Accession number: P43357
74	NY-ESO-1 protein	Accession number: P78358
75	LAGE-1a protein	Accession number: CAA11116
76	LAGE-1b protein	Accession number: CAA11117
77	PRAME protein	Accession number: NP 006106
78	PSA protein	Accession number: P07288
79	PSCA protein	Accession number: O43653
80	GP100 cds	Accession number: U20093
81	MAGE-1 cds	Accession number: M77481
82	MAGE-2 cds	Accession number: L18920
83	MAGE-3 cds	Accession number: U03735
84	NY-ESO-1 cDNA	Accession number: U87459
85	PRAME cDNA	Accession number: NM_006115
86	PSA cDNA	Accession number: NM_001648
87	PSCA cDNA	Accession number: AF043498
88	GP100 630-638	LPHSSSHWL
89	GP100 629-638	QLPHSSSHWL

90	GP100 614-622	LIYRRRLMK
91	GP100 613-622	SLIYRRRLMK
92	GP100 615-622	IYRRRLMK
93	GP100 630-638	LPHSSSHWL
94	GP100 629-638	QLPHSSSHWL
95	MAGE-1 95-102	ESLFRAVI
96	MAGE-1 93-102	ILESLFRAVI
97	MAGE-1 93-101	ILESLFRAV
98	MAGE-1 92-101	CILESLFRAV
99	MAGE-1 92-100	CILESLFRA
100	MAGE-1 263-271	EFLWGPRAL
101	MAGE-1 264-271	FLWGPRAL
102	MAGE-1 264-273	FLWGPRALAE
103	MAGE-1 265-274	LWGPRALAET
104	MAGE-1 268-276	PRALAETSY
105	MAGE-1 267-276	GPRALAETSY
106	MAGE-1 269-277	RALAETSYV
107	MAGE-1 271-279	LAETSYVKV
108	MAGE-1 270-279	ALAETSYVKV
109	MAGE-1 272-280	AETSYVKVL
110	MAGE-1 271-280	LAETSYVKVL
111	MAGE-1 274-282	TSYVKVLEY
112	MAGE-1 273-282	ETSYVKVLEY
113	MAGE-1 278-286	KVLEYVIKV
114	MAGE-1 168-177	SYVLVTCLGL
115	MAGE-1 169-177	YVLVTCLGL
116	MAGE-1 170-177	VLVTCLGL
117	MAGE-1 240-248	TQDLVQEKY
118	MAGE-1 239-248	LTQDLVQEKY
119	MAGE-1 232-240	YGEPRKLLT
120	MAGE-1 243-251	LVQEKYLEY
121	MAGE-1 242-251	DLVQEKYLEY
122	MAGE-1 230-238	SAYGEPRKL
123	MAGE-1 278-286	KVLEYVIKV
124	MAGE-1 277-286	VKVLEYVIKV
125	MAGE-1 276-284	YVKVLEYVI
126	MAGE-1 274-282	TSYVKVLEY
127	MAGE-1 273-282	ETSYVKVLEY
128	MAGE-1 283-291	VIKVSARVR
129	MAGE-1 282-291	YVIKVSARVR
130	MAGE-2 115-122	ELVHFLLL
131	MAGE-2 113-122	MVELVHFLLL

132	MAGE-2 109-116	ISRKMVEL
133	MAGE-2 108-116	AISRKMVEL
134	MAGE-2 107-116	AAISRKMVEL
135	MAGE-2 112-120	KMVELVHFL
136	MAGE-2 109-117	ISRKMVELV
137	MAGE-2 108-117	AISRKMVELV
138	MAGE-2 116-124	LVHFLLLKY
139	MAGE-2 115-124	ELVHFLLLKY
140	MAGE-2 111-119	RKMVELVHF
141	MAGE-2 158-166	LQLVFGIEV
142	MAGE-2 157-166	YLQLVFGIEV
143	MAGE-2 159-167	QLVFGIEVV
144	MAGE-2 158-167	LQLVFGIEVV
145	MAGE-2 164-172	IEVVEVVPI
146	MAGE-2 163-172	GIEVVEVVPI
147	MAGE-2 162-170	FGIEVVEVV
148	MAGE-2 154-162	ASEYLQLVF
149	MAGE-2 153-162	KASEYLQLVF
150	MAGE-2 218-225	EEKIWEEL
151	MAGE-2 216-225	APEEKIWEEL
152	MAGE-2 216-223	APEEKIWE
153	MAGE-2 220-228	KIWEELSML
154	MAGE-2 219-228	EKIWEELSML
155	MAGE-2 271-278	FLWGPRAL
156	MAGE-2 271-279	FLWGPRALI
157	MAGE-2 278-286	LIETSYVKV
158	MAGE-2 277-286	ALIETSYVKV
159	MAGE-2 276-284	RALIETSYV
160	MAGE-2 279-287	IETSYVKVL
161	MAGE-2 278-287	LIETSYVKVL
162	MAGE-3 271-278	FLWGPRAL
163	MAGE-3 270-278	EFLWGPRAL
164	MAGE-3 271-279	FLWGPRALV
165	MAGE-3 276-284	RALVETSYV
166	MAGE-3 272-280	LWGPRALVE
167	MAGE-3 271-280	FLWGPRALVE
168	MAGE-3 27 2-281	LWGPRALVET
169	NY-ESO-1 82-90	GPESRLLEF
170	NY-ESO-1 83-91	PESRLLEFY
171	NY-ESO-1 82-91	GPESRLLEFY
172	NY-ESO-1 84-92	ESRLLEFYL
173	NY-ESO-1 86-94	RLLEFYLAM

174	NY-ESO-1 88-96	LEFYLAMPF
175	NY-ESO-1 87-96	LLEFYLAMPF
176	NY-ESO-1 93-102	AMPFATPMEA
177	NY-ESO-1 94-102	MPFATPMEA
178	NY-ESO-1 115-123	PLPVPGVLL
179	NY-ESO-1 114-123	PPLPVPGVLL
180	NY-ESO-1 116-123	LPVPGVLL
181	NY-ESO-1 103-112	ELARRSLAQD
182	NY-ESO-1 118-126	VPGVLLKEF
183	NY-ESO-1 117-126	PVPGVLLKEF
184	NY-ESO-1 116-123	LPVPGVLL
185	NY-ESO-1 127-135	TVSGNILTI
186	NY-ESO-1 126-135	FTVSGNILTI
187	NY-ESO-1 120-128	GVLLKEFTV
188	NY-ESO-1 121-130	VLLKEFTVSG
189	NY-ESO-1 122-130	LLKEFTVSG
190	NY-ESO-1 118-126	VPGVLLKEF
191	NY-ESO-1 117-126	PVPGVLLKEF
192	NY-ESO-1 139-147	AADHRQLQL
193	NY-ESO-1 148-156	SISSCLQQL
194	NY-ESO-1 147-156	LSISSCLQQL
195	NY-ESO-1 138-147	TAADHRQLQL
196	NY-ESO-1 161-169	WITQCFLPV
197	NY-ESO-1 157-165	SLLMWITQC
198	NY-ESO-1 150-158	SSCLQQLSL
199	NY-ESO-1 154-162	QQLSLLMWI
200	NY-ESO-1 151-159	SCLQQLSLL
201	NY-ESO-1 150-159	SSCLQQLSLL
202	NY-ESO-1 163-171	TQCFLPVFL
203	NY-ESO-1 162-171	ITQCFLPVFL
204	PRAME 219-227	PMQDIKMIL
205	PRAME 218-227	MPMQDIKMIL
206	PRAME 428-436	QHLIGLSNL
207	PRAME 427-436	LQHLIGLSNL
208	PRAME 429-436	HLIGLSNL
209	PRAME 431-439	IGLSNLTHV
210	PRAME 430-439	LIGLSNLTHV
211	PSA 53-61	VLVHPQWVL
212	PSA 52-61	GVLVHPQWVL
213	PSA 52-60	GVLVHPQWV
214	PSA 59-67	WVLTAAHCI
215	PSA 54-63	LVHPQWVLTA

216	PSA 53-62	VLVHPQWVLT
217	PSA 54-62	LVHPQWVLT
218	PSA 66-73	CIRNKSVI
219	PSA 65-73	HCIRNKSVI
220	PSA 56-64	HPQWVLTAA
221	PSA 63-72	AAHCIRNKSV
222	PSCA 116-123	LLWGPGQL
223	PSCA 115-123	LLLWGPGQL
224	PSCA 114-123	GLLLWGPGQL
225	PSCA 99-107	ALQPAAAIL
226	PSCA 98-107	HALQPAAAIL
227	Tyr 128-137	APEKDKFFAY
228	Tyr 129-137	PEKDKFFAY
229	Tyr 130-138	EKDKFFAYL
230	Tyr 131-138	KDKFFAYL
231	Tyr 205-213	PAFLPWHRL
232	Tyr 204-213	APAFLPWHRL
233	Tyr 214-223	FLLRWEQEIQ
234	Tyr 212-220	RLFLLRWEQ
235	Tyr 191-200	GSEIWRDIDF
236	Tyr 192-200	SEIWRDIDF
237	Tyr 473-481	RIWSWLLGA
238	Tyr 476-484	SWLLGAAMV
239	Tyr 477-486	WLLGAAMVGA
240	Tyr 478-486	LLGAAMVGA
241	PSMA 4-12	LLHETDSAV
242	PSMA 13-21	ATARRPRWL
243	PSMA 53-61	TPKHNMKAF
244	PSMA 64-73	ELKAENIKKF
245	PSMA 69-77	NIKKFLH[1]NF
246	PSMA 68-77	ENIKKFLH[1]NF
247	PSMA 220-228	AGAKGVILY
248	PSMA 468-477	PLMYSLVHNL
249	PSMA 469-477	LMYSLVHNL
250	PSMA 463-471	RVDCTPLMY
251	PSMA 465-473	DCTPLMYSL
252	PSMA 507-515	SGMPRISKL
253	PSMA 506-515	FSGMPRISKL
254	NY-ESO-1 136-163	RLTAADHRQLQLSISSCLQQLSLLMWIT
255	NY-ESO-1 150-177	SSCLQQLSLLMWITQCFLPVFLAQPPSG

[1] This H was reported as Y in the SWISSPROT database.

[r]The amino acid at position 274 may be Pro or Leu depending upon the database. The particular analysis presented herein used the Pro.

Table 1C. SEQ ID NOS.* including epitopes in Example14.

SEQ ID NO.	IDENTITY	SEQUENCE
256	Mage-1 125-132	KAEMLESV
257	Mage-1 124-132	TKAEMLESV
258	Mage-1 123-132	VTKAEMLESV
259	Mage-1 128-136	MLESVIKNY
260	Mage-1 127-136	EMLESVIKNY
261	Mage-1 125-133	KAEMLESVI
262	Mage-1 146-153	KASESLQL
263	Mage-1 145-153	GKASESLQL
264	Mage-1 147-155	ASESLQLVF
265	Mage-1 153-161	LVFGIDVKE
266	Mage-1 114-121	LLKYRARE
267	Mage-1 106-113	VADLVGFL
268	Mage-1 105-113	KVADLVGFL
269	Mage-1 107-115	ADLVGFLLL
270	Mage-1 106-115	VADLVGFLLL
271	Mage-1 114-123	LLKYRAREPV
272	Mage-3 278-286	LVETSYVKV
273	Mage-3 277-286	ALVETSYVKV
274	Mage-3 285-293	KVLHHMVKI
275	Mage-3 283-291	YVKVLHHMV
276	Mage-3 275-283	PRALVETSY
277	Mage-3 274-283	GPRALVETSY
278	Mage-3 278-287	LVETSYVKVL
279	ED-B 4'-5	TIIPEVPQL
280	ED-B 5'-5	DTIIPEVPQL
281	ED-B 1-10	EVPQLTDLSF
282	ED-B 23-30	TPLNSSTI
283	ED-B 18-25	IGLRWTPL
284	ED-B 17-25	SIGLRWTPL
285	ED-B 25-33	LNSSTIIGY
286	ED-B 24-33	PLNSSTIIGY
287	ED-B 23-31	TPLNSSTII
288	ED-B 31-38	IGYRITVV
289	ED-B 30-38	IIGYRITVV
290	ED-B 29-38	TIIGYRITVV
291	ED-B 31-39	IGYRITVVA
292	ED-B 30-39	IIGYRITVVA
293	CEA 184-191	SLPVSPRL
294	CEA 183-191	QSLPVSPRL
295	CEA 186-193	PVSPRLQL
296	CEA 185-193	LPVSPRLQL
297	CEA 184-193	SLPVSPRLQL
298	CEA 185-192	LPVSPRLQ
299	CEA 192-200	QLSNGNRTL

300	CEA 191-200	LQLSNGNRTL
301	CEA 179-187	WVNNQSLPV
302	CEA 186-194	PVSPRLQLS
303	CEA 362-369	SLPVSPRL
304	CEA 361-369	QSLPVSPRL
305	CEA 364-371	PVSPRLQL
306	CEA 363-371	LPVSPRLQL
307	CEA 362-371	SLPVSPRLQL
308	CEA 363-370	LPVSPRLQ
309	CEA 370-378	QLSNDNRTL
310	CEA 369-378	LQLSNDNRTL
311	CEA 357-365	WVNNQSLPV
312	CEA 360-368	NQSLPVSPR
313	CEA 540-547	SLPVSPRL
314	CEA 539-547	QSLPVSPRL
315	CEA 542-549	PVSPRLQL
316	CEA 541-549	LPVSPRLQL
317	CEA 540-549	SLPVSPRLQL
318	CEA 541-548	LPVSPRLQ
319	CEA 548-556	QLSNGNRTL
320	CEA 547-556	LQLSNGNRTL
321	CEA 535-543	WVNGQSLPV
322	CEA 533-541	LWWVNGQSL
323	CEA 532-541	YLWWVNGQSL
324	CEA 538-546	GQSLPVSPR
325	Her-2 30-37	DMKLRLPA
326	Her-2 28-37	GTDMKLRLPA
327	Her-2 42-49	HLDMLRHL
328	Her-2 41-49	THLDMLRHL
329	Her-2 40-49	ETHLDMLRHL
330	Her-2 36-43	PASPETHL
331	Her-2 35-43	LPASPETHL
332	Her-2 34-43	RLPASPETHL
333	Her-2 38-46	SPETHLDML
334	Her-2 37-46	ASPETHLDML
335	Her-2 42-50	HLDMLRHLY
336	Her-2 41-50	THLDMLRHLY
337	Her-2 719-726	ELRKVKVL
338	Her-2 718-726	TELRKVKVL
339	Her-2 717-726	ETELRKVKVL
340	Her-2 715-723	LKETELRKV
341	Her-2 714-723	ILKETELRKV
342	Her-2 712-720	MRILKETEL
343	Her-2 711-720	QMRILKETEL
344	Her-2 717-725	ETELRKVKV
345	Her-2 716-725	KETELRKVKV
346	Her-2 706-714	MPNQAQMRI
347	Her-2 705-714	AMPNQAQMRI
348	Her-2 706-715	MPNQAQMRIL
349	HER-2 966-973	RPRFRELV

350	HER-2 965-973	CRPRFRELV
351	HER-2 968-976	RFRELVSEF
352	HER-2 967-976	PRFRELVSEF
353	HER-2 964-972	ECRPRFREL
354	NY-ESO-1 67-75	GAASGLNGC
355	NY-ESO-1 52-60	RASGPGGGA
356	NY-ESO-1 64-72	PHGGAASGL
357	NY-ESO-1 63-72	GPHGGAASGL
358	NY-ESO-1 60-69	APRGPHGGAA
359	PRAME 112-119	VRPRRWKL
360	PRAME 111-119	EVRPRRWKL
361	PRAME 113-121	RPRRWKLQV
362	PRAME 114-122	PRRWKLQVL
363	PRAME 113-122	RPRRWKLQVL
364	PRAME 116-124	RWKLQVLDL
365	PRAME 115-124	RRWKLQVLDL
366	PRAME 174-182	PVEVLVDLF
367	PRAME 199-206	VKRKKNVL
368	PRAME 198-206	KVKRKKNVL
369	PRAME 197-206	EKVKRKKNVL
370	PRAME 198-205	KVKRKKNV
371	PRAME 201-208	RKKNVLRL
372	PRAME 200-208	KRKKNVLRL
373	PRAME 199-208	VKRKKNVLRL
374	PRAME 189-196	DELFSYLI
375	PRAME 205-213	VLRLCCKKL
376	PRAME 204-213	NVLRLCCKKL
377	PRAME 194-202	YLIEKVKRK
378	PRAME 74-81	QAWPFTCL
379	PRAME 73-81	VQAWPFTCL
380	PRAME 72-81	MVQAWPFTCL
381	PRAME 81-88	LPLGVLMK
382	PRAME 80-88	CLPLGVLMK
383	PRAME 79-88	TCLPLGVLMK
384	PRAME 84-92	GVLMKGQHL
385	PRAME 81-89	LPLGVLMKG
386	PRAME 80-89	CLPLGVLMKG
387	PRAME 76-85	WPFTCLPLGV
388	PRAME 51-59	ELFPPLFMA
389	PRAME 49-57	PRELFPPLF
390	PRAME 48-57	LPRELFPPLF
391	PRAME 50-58	RELFPPLFM
392	PRAME 49-58	PRELFPPLFM
393	PSA 239-246	RPSLYTKV
394	PSA 238-246	ERPSLYTKV
395	PSA 236-243	LPERPSLY
396	PSA 235-243	ALPERPSLY
397	PSA 241-249	SLYTKVVHY
398	PSA 240-249	PSLYTKVVHY
399	PSA 239-247	RPSLYTKVV

400	PSMA 211-218	GNKVKNAQ
401	PSMA 202-209	IARYGKVF
402	PSMA 217-225	AQLAGAKGV
403	PSMA 207-215	KVFRGNKVK
404	PSMA 211-219	GNKVKNAQL
405	PSMA 269-277	TPGYPANEY
406	PSMA 268-277	LTPGYPANEY
407	PSMA 271-279	GYPANEYAY
408	PSMA 270-279	PGYPANEYAY
409	PSMA 266-274	DPLTPGYPA
410	PSMA 492-500	SLYESWTKK
411	PSMA 491-500	KSLYESWTKK
412	PSMA 486-494	EGFEGKSLY
413	PSMA 485-494	DEGFEGKSLY
414	PSMA 498-506	TKKSPSPEF
415	PSMA 497-506	WTKKSPSPEF
416	PSMA 492-501	SLYESWTKKS
417	PSMA 725-732	WGEVKRQI
418	PSMA 724-732	AWGEVKRQI
419	PSMA 723-732	KAWGEVKRQI
420	PSMA 723-730	KAWGEVKR
421	PSMA 722-730	SKAWGEVKR
422	PSMA 731-739	QIYVAAFTV
423	PSMA 733-741	YVAAFTVQA
424	PSMA 725-733	WGEVKRQIY
425	PSMA 727-735	EVKRQIYVA
426	PSMA 738-746	TVQAAAETL
427	PSMA 737-746	FTVQAAAETL
428	PSMA 729-737	KRQIYVAAF
429	PSMA 721-729	PSKAWGEVK
430	PSMA 723-731	KAWGEVKRQ
431	PSMA 100-108	WKEFGLDSV
432	PSMA 99-108	QWKEFGLDSV
433	PSMA 102-111	EFGLDSVELA
434	SCP-1 126-134	ELRQKESKL
435	SCP-1 125-134	AELRQKESKL
436	SCP-1 133-141	KLQENRKII
437	SCP-1 298-305	QLEEKTKL
438	SCP-1 297-305	NQLEEKTKL
439	SCP-1 288-296	LLEESRDKV
440	SCP-1 287-296	FLLEESRDKV
441	SCP-1 291-299	ESRDKVNQL
442	SCP-1 290-299	EESRDKVNQL
443	SCP-1 475-483	EKEVHDLEY
444	SCP-1 474-483	REKEVHDLEY
445	SCP-1 480-488	DLEYSYCHY
446	SCP-1 477-485	EVHDLEYSY
447	SCP-1 477-486	EVHDLEYSYC
448	SCP-1 502-509	KLSSKREL
449	SCP-1 508-515	ELKNTEYF

450	SCP-1 507-515	RELKNTEYF
451	SCP-1 496-503	KRGQRPKL
452	SCP-1 494-503	LPKRGQRPKL
453	SCP-1 509-517	LKNTEYFTL
454	SCP-1 508-517	ELKNTEYFTL
455	SCP-1 506-514	KRELKNTEY
456	SCP-1 502-510	KLSSKRELK
457	SCP-1 498-506	GQRPKLSSK
458	SCP-1 497-506	RGQRPKLSSK
459	SCP-1 500-508	RPKLSSKRE
460	SCP-1 573-580	LEYVREEL
461	SCP-1 572-580	ELEYVREEL
462	SCP-1 571-580	NELEYVREEL
463	SCP-1 579-587	ELKQKREDEV
464	SCP-1 575-583	YVREELKQK
465	SCP-1 632-640	QLNVYEIKV
466	SCP-1 630-638	SKQLNVYEI
467	SCP-1 628-636	AESKQLNVY
468	SCP-1 627-636	TAESKQLNVY
469	SCP-1 638-645	IKVNKLEL
470	SCP-1 637-645	EIKVNKLEL
471	SCP-1 636-645	YEIKVNKLEL
472	SCP-1 642-650	KLELELESA
473	SCP-1 635-643	VYEIKVNKL
474	SCP-1 634-643	NVYEIKVNKL
475	SCP-1 646-654	ELESAKQKF
476	SCP-1 642-650	KLELELESA
477	SCP-1 646-654	ELESAKQKF
478	SCP-1 771-778	KEKLKREA
479	SCP-1 777-785	EAKENTATL
480	SCP-1 776-785	REAKENTATL
481	SCP-1 773-782	KLKREAKENT
482	SCP-1 112-119	EAEKIKKW
483	SCP-1 101-109	GLSRVYSKL
484	SCP-1 100-109	EGLSRVYSKL
485	SCP-1 108-116	KLYKEAEKI
486	SCP-1 98-106	NSEGLSRVY
487	SCP-1 97-106	ENSEGLSRVY
488	SCP-1 102-110	LSRVYSKLY
489	SCP-1 101-110	GLSRVYSKLY
490	SCP-1 96-105	LENSEGLSRV
491	SCP-1 108-117	KLYKEAEKIK
492	SCP-1 949-956	REDRWAVI
493	SCP-1 948-956	MREDRWAVI
494	SCP-1 947-956	KMREDRWAVI
495	SCP-1 947-955	KMREDRWAV
496	SCP-1 934-942	TTPGSTLKF
497	SCP-1 933-942	LTTPGSTLKF
498	SCP-1 937-945	GSTLKGAI
499	SCP-1 945-953	IRKMREDRW

500	SCP-1 236-243	RLEMHFKL
501	SCP-1 235-243	SRLEMHFKL
502	SCP-1 242-250	KLKEDYEKI
503	SCP-1 249-257	KIQHLEQEY
504	SCP-1 248-257	EKIQHLEQEY
505	SCP-1 233-242	ENSRLEMHF
506	SCP-1 236-245	RLEMHFKLKE
507	SCP-1 324-331	LEDIKVSL
508	SCP-1 323-331	ELEDIKVSL
509	SCP-1 322-331	KELEDIKVSL
510	SCP-1 320-327	LTKELEDI
511	SCP-1 319-327	HLTKELEDI
512	SCP-1 330-338	SLQRSVSTQ
513	SCP-1 321-329	TKELEDIKV
514	SCP-1 320-329	LTKELEDIKV
515	SCP-1 326-335	DIKVSLQRSV
516	SCP-1 281-288	KMKDLTFL
517	SCP-1 280-288	NKMKDLTFL
518	SCP-1 279-288	ENKMKDLTFL
519	SCP-1 288-296	LLEESRDKV
520	SCP-1 287-296	FLLEESRDKV
521	SCP-1 291-299	ESRDKVNQL
522	SCP-1 290-299	EESRDKVNQL
523	SCP-1 277-285	EKENKMKDL
524	SCP-1 276-285	TEKENKMKDL
525	SCP-1 279-287	ENKMKDLTF
526	SCP-1 218-225	IEKMITAF
527	SCP-1 217-225	NIEKMITAF
528	SCP-1 216-225	SNIEKMITAF
529	SCP-1 223-230	TAFEELRV
530	SCP-1 222-230	ITAFEELRV
531	SCP-1 221-230	MITAFEELRV
532	SCP-1 220-228	KMITAFEEL
533	SCP-1 219-228	EKMITAFEEL
534	SCP-1 227-235	ELRVQAENS
535	SCP-1 213-222	DLNSNIEKMI
536	SCP-1 837-844	WTSAKNTL
537	SCP-1 846-854	TPLPKAYTV
538	SCP-1 845-854	STPLPKAYTV
539	SCP-1 844-852	LSTPLPKAY
540	SCP-1 843-852	TLSTPLPKAY
541	SCP-1 842-850	NTLSTPLPK
542	SCP-1 841-850	KNTLSTPLPK
543	SCP-1 828-835	ISKDKRDY
544	SCP-1 826-835	HGISKDKRDY
545	SCP-1 832-840	KRDYLWTSA
546	SCP-1 829-838	SKDKRDYLWT
547	SCP-1 279-286	ENKMKDLT
548	SCP-1 260-268	EINDKEKQV
549	SCP-1 274-282	QITEKENKM

550	SCP-1 269-277	SLLLIQITE
551	SCP-1 453-460	FEKIAEEL
552	SCP-1 452-460	QFEKIAEEL
553	SCP-1 451-460	KQFEKIAEEL
554	SCP-1 449-456	DNKQFEKI
555	SCP-1 448-456	YDNKQFEKI
556	SCP-1 447-456	LYDNKQFEKI
557	SCP-1 440-447	LGEKETLL
558	SCP-1 439-447	VLGEKETLL
559	SCP-1 438-447	KVLGEKETLL
560	SCP-1 390-398	LLRTEQQRL
561	SCP-1 389-398	ELLRTEQQRL
562	SCP-1 393-401	TEQQRLENY
563	SCP-1 392-401	RTEQQRLENY
564	SCP-1 402-410	EDQLIILTM
565	SCP-1 397-406	RLENYEDQLI
566	SCP-1 368-375	KARAAHSF
567	SCP-1 376-384	VVTEFETTV
568	SCP-1 375-384	FVVTEFETTV
569	SCP-1 377-385	VTEFETTVC
570	SCP-1 376-385	VVTEFETTVC
571	SCP-1 344-352	DLQIATNTI
572	SCP-1 347-355	IATNTICQL
573	SCP-1 346-355	QIATNTICQL
574	SSX4 57-65	VMTKLGFKY
575	SSX4 53-61	LNYEVMTKL
576	SSX4 52-61	KLNYEVMTKL
577	SSX4 66-74	TLPPFMRSK
578	SSX4 110-118	KIMPKKPAE
579	SSX4 103-112	SLQRIFPKIM
580	Tyr 463-471	YIKSYLEQA
581	Tyr 459-467	SFQDYIKSY
582	Tyr 458-467	DSFQDYIKSY
583	Tyr 507-514	LPEEKQPL
584	Tyr 506-514	QLPEEKQPL
585	Tyr 505-514	KQLPEEKQPL
586	Tyr 507-515	LPEEKQPLL
587	Tyr 506-515	QLPEEKQPLL
588	Tyr 497-505	SLLCRHKRK
589	ED-B domain of Fibronectin	EVPQLTDLSFVDITDSSIGLRWTPLNSSTIIGYRI TVVAAGEGIPIFEDFVDSSVGYYTVTGLEPGID YDISVITLINGGESAPTTLTQQT
590	ED-B domain of Fibronectin with flanking sequence from Fribronectin	CTFDNLSPGLEYNVSVYTVKDDKESVPISDTIIP EVPQLTDLSFVDITDSSIGLRWTPLNSSTIIGYRI TVVAAGEGIPIFEDFVDSSVGYYTVTGLEPGID YDISVITLINGGESAPTTLTQQT AVPPPTDLRFTNIGPDTMRVTW
591	ED-B domain of Fibronectin cds	Accession number: X07717
592	CEA protein	Accession number: P06731
593	CEA cDNA	Accession number: NM_004363

594	Her2/Neu protein	Accession number: P04626
595	Her2/Neu cDNA	Accession number: M11730
596	SCP-1 protein	Accession number: Q15431
597	SCP-1 cDNA	Accession number: X95654
598	SSX-4 protein	Accession number: O60224
599	SSX-4 cDNA	Accession number: NM_005636

*Any of SEQ ID NOS. 1, 8, 9, 11-23, 26-29, 32-44, 47-54, 56-63, 66-68 88-253, and 256-588 can be useful as epitopes in any of the various embodiments of the invention. Any of SEQ ID NOS. 10, 30, 31, 45, 46, 55, 64, 65, 69, 254, and 255 can be useful as sequences containing epitopes or epitope clusters, as described in various embodiments of the invention.

**All accession numbers used here and throughout can be accessed through the NCBI databases, for example, through the Entrez seek and retrieval system on the world wide web.

Note that the following discussion sets forth the inventors' understanding of the operation of the invention. However, it is not intended that this discussion limit the patent to any particular theory of operation not set forth in the claims.

In pursuing the development of epitope vaccines others have generated lists of predicted epitopes based on MHC binding motifs. Such peptides can be immunogenic, but may not correspond to any naturally produced antigenic fragment. Therefore, whole antigen will not elicit a similar response or sensitize a target cell to cytolysis by CTL. Therefore such lists do not differentiate between those sequences that can be useful as vaccines and those that cannot. Efforts to determine which of these predicted epitopes are in fact naturally produced have often relied on screening their reactivity with tumor infiltrating lymphocytes (TIL). However, TIL are strongly biased to recognize immune epitopes whereas tumors (and chronically infected cells) will generally present housekeeping epitopes. Thus, unless the epitope is produced by both the housekeeping and immuno- proteasomes, the target cell will generally not be recognized by CTL induced with TIL-identified epitopes. The epitopes of the present invention, in contrast, are generated by the action of a specified proteasome, indicating that they can be naturally produced, and enabling their appropriate use. The importance of the distinction between housekeeping and immune epitopes to vaccine design is more fully set forth in PCT publication WO 01/82963A2.

The epitopes of the invention include or encode polypeptide fragments of TAAs that are precursors or products of proteasomal cleavage by a housekeeping or immune proteasome, and that contain or consist of a sequence having a known or predicted affinity for at least one allele of MHC I. In some embodiments, the epitopes include or encode a polypeptide of about 6 to 25 amino acids in length, preferably about 7 to 20 amino acids in length, more preferably about 8 to 15 amino acids in length, and still more preferably 9 or 10 amino acids in length. However, it is understood that the polypeptides can be larger as long as N-terminal trimming can produce the MHC epitope or that they do not contain sequences that cause the polypeptides to be directed away from the proteasome or to be destroyed by the proteasome. For immune epitopes, if the larger

peptides do not contain such sequences, they can be processed in the pAPC by the immune proteasome. Housekeeping epitopes may also be embedded in longer sequences provided that the sequence is adapted to facilitate liberation of the epitope's C-terminus by action of the immunoproteasome. The foregoing discussion has assumed that processing of longer epitopes proceeds through action of the immunoproteasome of the pAPC. However, processing can also be accomplished through the contrivance of some other mechanism, such as providing an exogenous protease activity and a sequence adapted so that action of the protease liberates the MHC epitope. The sequences of these epitopes can be subjected to computer analysis in order to calculate physical, biochemical, immunologic, or molecular genetic properties such as mass, isoelectric point, predicted mobility in electrophoresis, predicted binding to other MHC molecules, melting temperature of nucleic acid probes, reverse translations, similarity or homology to other sequences, and the like.

In constructing the polynucleotides encoding the polypeptide epitopes of the invention, the gene sequence of the associated TAA can be used, or the polynucleotide can be assembled from any of the corresponding codons. For a 10 amino acid epitope this can constitute on the order of 10^6 different sequences, depending on the particular amino acid composition. While large, this is a distinct and readily definable set representing a miniscule fraction of the $>10^{18}$ possible polynucleotides of this length, and thus in some embodiments, equivalents of a particular sequence disclosed herein encompass such distinct and readily definable variations on the listed sequence. In choosing a particular one of these sequences to use in a vaccine, considerations such as codon usage, self-complementarity, restriction sites, chemical stability, etc. can be used as will be apparent to one skilled in the art.

The invention contemplates producing peptide epitopes. Specifically these epitopes are derived from the sequence of a TAA, and have known or predicted affinity for at least one allele of MHC I. Such epitopes are typically identical to those produced on target cells or pAPCs.

Compositions Containing Active Epitopes

Embodiments of the present invention provide polypeptide compositions, including vaccines, therapeutics, diagnostics, pharmacological and pharmaceutical compositions. The various compositions include newly identified epitopes of TAAs, as well as variants of these epitopes. Other embodiments of the invention provide polynucleotides encoding the polypeptide epitopes of the invention. The invention further provides vectors for expression of the polypeptide epitopes for purification. In addition, the invention provides vectors for the expression of the polypeptide epitopes in an APC for use as an anti-tumor vaccine. Any of the epitopes or antigens, or nucleic acids encoding the same, from Table 1 can be used. Other embodiments relate to methods of making and using the various compositions.

A general architecture for a class I MHC-binding epitope can be described, and has been reviewed more extensively in Madden, D.R. *Annu. Rev. Immunol.* 13:587-622, 1995. Much of the binding energy arises from main chain contacts between conserved residues in the MHC molecule and the N- and C-termini of the peptide. Additional main chain contacts are made but vary among MHC alleles. Sequence specificity is conferred by side chain contacts of so-called anchor residues with pockets that, again, vary among MHC alleles. Anchor residues can be divided into primary and secondary. Primary anchor positions exhibit strong preferences for relatively well-defined sets of amino acid residues. Secondary positions show weaker and/or less well-defined preferences that can often be better described in terms of less favored, rather than more favored, residues. Additionally, residues in some secondary anchor positions are not always positioned to contact the pocket on the MHC molecule at all. Thus, a subset of peptides exists that bind to a particular MHC molecule and have a side chain-pocket contact at the position in question and another subset exists that show binding to the same MHC molecule that does not depend on the conformation the peptide assumes in the peptide-binding groove of the MHC molecule. The C-terminal residue (P ; omega) is preferably a primary anchor residue. For many of the better studied HLA molecules (e.g. A2, A68, B27, B7, B35, and B53) the second position (P2) is also an anchor residue. However, central anchor residues have also been observed including P3 and P5 in HLA-B8, as well as P5 and P (omega)-3 in the murine MHC molecules H-2D^b and H-2K^b, respectively. Since more stable binding will generally improve immunogenicity, anchor residues are preferably conserved or optimized in the design of variants, regardless of their position.

Because the anchor residues are generally located near the ends of the epitope, the peptide can buckle upward out of the peptide-binding groove allowing some variation in length. Epitopes ranging from 8-11 amino acids have been found for HLA-A68, and up to 13 amino acids for HLA-A2. In addition to length variation between the anchor positions, single residue truncations and extensions have been reported and the N- and C-termini, respectively. Of the non-anchor residues, some point up out of the groove, making no contact with the MHC molecule but being available to contact the TCR, very often P1, P4, and P (omega)-1 for HLA-A2. Others of the non-anchor residues can become interposed between the upper edges of the peptide-binding groove and the TCR, contacting both. The exact positioning of these side chain residues, and thus their effects on binding, MHC fine conformation, and ultimately immunogenicity, are highly sequence dependent. For an epitope to be highly immunogenic it must not only promote stable enough TCR binding for activation to occur, but the TCR must also have a high enough off-rate that multiple TCR molecules can interact sequentially with the same peptide-MHC complex (Kalergis, A.M. et al., *Nature Immunol.* 2:229-234, 2001. Thus, without further information about the ternary complex,

both conservative and non-conservative substitutions at these positions merit consideration when designing variants.

The polypeptide epitope variants can be made, for example, using any of the techniques and guidelines for conservative and non-conservative mutations. Variants can be derived from substitution, deletion or insertion of one or more amino acids as compared with the native sequence. Amino acid substitutions can be the result of replacing one amino acid with another amino acid having similar structural and/or chemical properties, such as the replacement of a threonine with a serine, for example. Such replacements are referred to as conservative amino acid replacements, and all appropriate conservative amino acid replacements are considered to be embodiments of one invention. Insertions or deletions can optionally be in the range of about 1 to 4, preferably 1 to 2, amino acids. It is generally preferable to maintain the "anchor positions" of the peptide which are responsible for binding to the MHC molecule in question. Indeed, immunogenicity of peptides can be improved in many cases by substituting more preferred residues at the anchor positions (Franco, et al., *Nature Immunology*, 1(2):145-150, 2000. Immunogenicity of a peptide can also often be improved by substituting bulkier amino acids for small amino acids found in non-anchor positions while maintaining sufficient cross-reactivity with the original epitope to constitute a useful vaccine. The variation allowed can be determined by routine insertions, deletions or substitutions of amino acids in the sequence and testing the resulting variants for activity exhibited by the polypeptide epitope. Because the polypeptide epitope is often 9 amino acids, the substitutions preferably are made to the shortest active epitope, for example, an epitope of 9 amino acids.

Variants can also be made by adding any sequence onto the N-terminus of the polypeptide epitope variant. Such N-terminal additions can be from 1 amino acid up to at least 25 amino acids. Because peptide epitopes are often trimmed by N-terminal exopeptidases active in the pAPC, it is understood that variations in the added sequence can have no effect on the activity of the epitope. In preferred embodiments, the amino acid residues between the last upstream proteasomal cleavage site and the N-terminus of the MHC epitope do not include a proline residue. Serwold, T. at al., Nature Immunol. 2:644-651, 2001. Accordingly, effective epitopes can be generated from precursors larger than the preferred 9-mer class I motif.

Generally, peptides are useful to the extent that they correspond to epitopes actually displayed by MHC I on the surface of a target cell or a pACP. A single peptide can have varying affinities for different MHC molecules, binding some well, others adequately, and still others not appreciably (Table 2). MHC alleles have traditionally been grouped according to serologic reactivity which does not reflect the structure of the peptide-binding groove, which can differ among different alleles of the same type. Similarly, binding properties can be shared across types;

groups based on shared binding properties have been termed supertypes. There are numerous alleles of MHC I in the human population; epitopes specific to certain alleles can be selected based on the genotype of the patient.

Table 2.

Predicted Binding of Tyrosinase$_{207-216}$ (SEQ ID NO. 1) to Various MHC types

MHC I type	*Half time of dissociation (min)
A1	0.05
A*0201	1311.
A*0205	50.4
A3	2.7
A*1101 (part of the A3 supertype)	0.012
A24	6.0
B7	4.0
B8	8.0
B14 (part of the B27 supertype)	60.0
B*2702	0.9
B*2705	30.0
B*3501 (part of the B7 supertype)	2.0
B*4403	0.1
B*5101 (part of the B7 supertype)	26.0
B*5102	55.0
B*5801	0.20
B60	0.40
B62	2.0

*HLA Peptide Binding Predictions (world wide web hypertext transfer protocol "access at bimas.dcrt.nih.gov/molbio/hla_bin").

In further embodiments of the invention, the epitope, as peptide or encoding polynucleotide, can be administered as a pharmaceutical composition, such as, for example, a vaccine or an immunogenic composition, alone or in combination with various adjuvants, carriers, or excipients. It should be noted that although the term vaccine may be used throughout the discussion herein, the concepts can be applied and used with any other pharmaceutical composition, including those mentioned herein. Particularly advantageous adjuvants include various cytokines and oligonucleotides containing immunostimulatory sequences (as set forth in greater detail in the co-pending applications referenced herein). Additionally the polynucleotide encoded epitope can be contained in a virus (e.g. *vaccinia* or adenovirus) or in a microbial host cell (e.g. *Salmonella* or *Listeria monocytogenes*) which is then used as a vector for the polynucleotide (Dietrich, G. et al. Nat. Biotech. 16:181-185, 1998). Alternatively a pAPC can be transformed, *ex vivo*, to express the epitope, or pulsed with peptide epitope, to be itself administered as a vaccine. To increase efficiency of these processes, the encoded epitope can be carried by a viral or bacterial vector, or complexed with a ligand of a receptor found on pAPC. Similarly the peptide epitope can

be complexed with or conjugated to a pAPC ligand. A vaccine can be composed of more than a single epitope.

Particularly advantageous strategies for incorporating epitopes and/or epitope clusters, into a vaccine or pharmaceutical composition are disclosed in U.S. Patent Application No. 09/560,465 entitled "EPITOPE SYNCHRONIZATION IN ANTIGEN PRESENTING CELLS," filed on April 28, 2000. Epitope clusters for use in connection with this invention are disclosed in U.S. Patent Application No. 09/561,571 entitled "EPITOPE CLUSTERS," filed on April 28, 2000.

Preferred embodiments of the present invention are directed to vaccines and methods for causing a pAPC or population of pAPCs to present housekeeping epitopes that correspond to the epitopes displayed on a particular target cell. Any of the epitopes or antigens in Table 1, can be used for example. In one embodiment, the housekeeping epitope is a TuAA epitope processed by the housekeeping proteasome of a particular tumor type. In another embodiment, the housekeeping epitope is a virus-associated epitope processed by the housekeeping proteasome of a cell infected with a virus. This facilitates a specific T cell response to the target cells. Concurrent expression by the pAPCs of multiple epitopes, corresponding to different induction states (pre- and post-attack), can drive a CTL response effective against target cells as they display either housekeeping epitopes or immune epitopes.

By having both housekeeping and immune epitopes present on the pAPC, this embodiment can optimize the cytotoxic T cell response to a target cell. With dual epitope expression, the pAPCs can continue to sustain a CTL response to the immune-type epitope when the tumor cell switches from the housekeeping proteasome to the immune proteasome with induction by IFN, which, for example, may be produced by tumor-infiltrating CTLs.

In a preferred embodiment, immunization of a patient is with a vaccine that includes a housekeeping epitope. Many preferred TAAs are associated exclusively with a target cell, particularly in the case of infected cells. In another embodiment, many preferred TAAs are the result of deregulated gene expression in transformed cells, but are found also in tissues of the testis, ovaries and fetus. In another embodiment, useful TAAs are expressed at higher levels in the target cell than in other cells. In still other embodiments, TAAs are not differentially expressed in the target cell compare to other cells, but are still useful since they are involved in a particular function of the cell and differentiate the target cell from most other peripheral cells; in such embodiments, healthy cells also displaying the TAA may be collaterally attacked by the induced T cell response, but such collateral damage is considered to be far preferable to the condition caused by the target cell.

The vaccine contains a housekeeping epitope in a concentration effective to cause a pAPC or populations of pAPCs to display housekeeping epitopes. Advantageously, the vaccine can

include a plurality of housekeeping epitopes or one or more housekeeping epitopes optionally in combination with one or more immune epitopes. Formulations of the vaccine contain peptides and/or nucleic acids in a concentration sufficient to cause pAPCs to present the epitopes. The formulations preferably contain epitopes in a total concentration of about 1μg-1mg/100μl of vaccine preparation. Conventional dosages and dosing for peptide vaccines and/or nucleic acid vaccines can be used with the present invention, and such dosing regimens are well understood in the art. In one embodiment, a single dosage for an adult human may advantageously be from about 1 to about 5000 μl of such a composition, administered one time or multiple times, e.g., in 2, 3, 4 or more dosages separated by 1 week, 2 weeks, 1 month, or more. insulin pump delivers 1 ul per hour (lowest frequency) ref intranodal method patent.

The compositions and methods of the invention disclosed herein further contemplate incorporating adjuvants into the formulations in order to enhance the performance of the vaccines. Specifically, the addition of adjuvants to the formulations is designed to enhance the delivery or uptake of the epitopes by the pAPCs. The adjuvants contemplated by the present invention are known by those of skill in the art and include, for example, GMCSF, GCSF, IL-2, IL-12, BCG, tetanus toxoid, osteopontin, and ETA-1.

In some embodiments of the invention, the vaccines can include a recombinant organism, such as a virus, bacterium or parasite, genetically engineered to express an epitope in a host. For example, *Listeria monocytogenes*, a gram-positive, facultative intracellular bacterium, is a potent vector for targeting TuAAs to the immune system. In a preferred embodiment, this vector can be engineered to express a housekeeping epitope to induce therapeutic responses. The normal route of infection of this organism is through the gut and can be delivered orally. In another embodiment, an adenovirus (Ad) vector encoding a housekeeping epitope for a TuAA can be used to induce anti-virus or anti-tumor responses. Bone marrow-derived dendritic cells can be transduced with the virus construct and then injected, or the virus can be delivered directly via subcutaneous injection into an animal to induce potent T-cell responses. Another embodiment employs a recombinant vaccinia virus engineered to encode amino acid sequences corresponding to a housekeeping epitope for a TAA. Vaccinia viruses carrying constructs with the appropriate nucleotide substitutions in the form of a minigene construct can direct the expression of a housekeeping epitope, leading to a therapeutic T cell response against the epitope.

The immunization with DNA requires that APCs take up the DNA and express the encoded proteins or peptides. It is possible to encode a discrete class I peptide on the DNA. By immunizing with this construct, APCs can be caused to express a housekeeping epitope, which is then displayed on class I MHC on the surface of the cell for stimulating an appropriate CTL response. Constructs generally relying on termination of translation or non-proteasomal proteases

for generation of proper termini of housekeeping epitopes have been described in U.S. Patent application No. 09/561,572 entitled EXPRESSION VECTORS ENCODING EPITOPES OF TARGET-ASSOCIATED ANTIGENS, filed on April 28, 2000.

As mentioned, it can be desirable to express housekeeping peptides in the context of a larger protein. Processing can be detected even when a small number of amino acids are present beyond the terminus of an epitope. Small peptide hormones are usually proteolytically processed from longer translation products, often in the size range of approximately 60-120 amino acids. This fact has led some to assume that this is the minimum size that can be efficiently translated. In some embodiments, the housekeeping peptide can be embedded in a translation product of at least about 60 amino acids. In other embodiments the housekeeping peptide can be embedded in a translation product of at least about 50, 30, or 15 amino acids.

Due to differential proteasomal processing, the immune proteasome of the pAPC produces peptides that are different from those produced by the housekeeping proteasome in peripheral body cells. Thus, in expressing a housekeeping peptide in the context of a larger protein, it is preferably expressed in the APC in a context other than its full length native sequence, because, as a housekeeping epitope, it is generally only efficiently processed from the native protein by the housekeeping proteasome, which is not active in the APC. In order to encode the housekeeping epitope in a DNA sequence encoding a larger protein, it is useful to find flanking areas on either side of the sequence encoding the epitope that permit appropriate cleavage by the immune proteasome in order to liberate that housekeeping epitope. Altering flanking amino acid residues at the N-terminus and C-terminus of the desired housekeeping epitope can facilitate appropriate cleavage and generation of the housekeeping epitope in the APC. Sequences embedding housekeeping epitopes can be designed *de novo* and screened to determine which can be successfully processed by immune proteasomes to liberate housekeeping epitopes.

Alternatively, another strategy is very effective for identifying sequences allowing production of housekeeping epitopes in APC. A contiguous sequence of amino acids can be generated from head to tail arrangement of one or more housekeeping epitopes. A construct expressing this sequence is used to immunize an animal, and the resulting T cell response is evaluated to determine its specificity to one or more of the epitopes in the array. By definition, these immune responses indicate housekeeping epitopes that are processed in the pAPC effectively. The necessary flanking areas around this epitope are thereby defined. The use of flanking regions of about 4-6 amino acids on either side of the desired peptide can provide the necessary information to facilitate proteasome processing of the housekeeping epitope by the immune proteasome. Therefore, a sequence ensuring epitope synchronization of approximately 16-22 amino acids can be inserted into, or fused to, any protein sequence effectively to result in

that housekeeping epitope being produced in an APC. In alternate embodiments the whole head-to-tail array of epitopes, or just the epitopes immediately adjacent to the correctly processed housekeeping epitope can be similarly transferred from a test construct to a vaccine vector.

In a preferred embodiment, the housekeeping epitopes can be embedded between known immune epitopes, or segments of such, thereby providing an appropriate context for processing. The abutment of housekeeping and immune epitopes can generate the necessary context to enable the immune proteasome to liberate the housekeeping epitope, or a larger fragment, preferably including a correct C-terminus. It can be useful to screen constructs to verify that the desired epitope is produced. The abutment of housekeeping epitopes can generate a site cleavable by the immune proteasome. Some embodiments of the invention employ known epitopes to flank housekeeping epitopes in test substrates; in others, screening as described below are used whether the flanking regions are arbitrary sequences or mutants of the natural flanking sequence, and whether or not knowledge of proteasomal cleavage preferences are used in designing the substrates.

Cleavage at the mature N-terminus of the epitope, while advantageous, is not required, since a variety of N-terminal trimming activities exist in the cell that can generate the mature N-terminus of the epitope subsequent to proteasomal processing. It is preferred that such N-terminal extension be less than about 25 amino acids in length and it is further preferred that the extension have few or no proline residues. Preferably, in screening, consideration is given not only to cleavage at the ends of the epitope (or at least at its C-terminus), but consideration also can be given to ensure limited cleavage within the epitope.

Shotgun approaches can be used in designing test substrates and can increase the efficiency of screening. In one embodiment multiple epitopes can be assembled one after the other, with individual epitopes possibly appearing more than once. The substrate can be screened to determine which epitopes can be produced. In the case where a particular epitope is of concern a substrate can be designed in which it appears in multiple different contexts. When a single epitope appearing in more than one context is liberated from the substrate additional secondary test substrates, in which individual instances of the epitope are removed, disabled, or are unique, can be used to determine which are being liberated and truly constitute sequences ensuring epitope synchronization.

Several readily practicable screens exist. A preferred *in vitro* screen utilizes proteasomal digestion analysis, using purified immune proteasomes, to determine if the desired housekeeping epitope can be liberated from a synthetic peptide embodying the sequence in question. The position of the cleavages obtained can be determined by techniques such as mass spectrometry, HPLC, and N-terminal pool sequencing; as described in greater detail in U. S. Patent Applications entitled METHOD OF EPITOPE DISCOVERY, EPITOPE SYNCHRONIZATION IN ANTIGEN

PRESENTING CELLS, two Provisional U. S. Patent Applications entitled EPITOPE SEQUENCES.

Alternatively, *in vivo* screens such as immunization or target sensitization can be employed. For immunization a nucleic acid construct capable of expressing the sequence in question is used. Harvested CTL can be tested for their ability to recognize target cells presenting the housekeeping epitope in question. Such targets cells are most readily obtained by pulsing cells expressing the appropriate MHC molecule with synthetic peptide embodying the mature housekeeping epitope. Alternatively, cells known to express housekeeping proteasome and the antigen from which the housekeeping epitope is derived, either endogenously or through genetic engineering, can be used. To use target sensitization as a screen, CTL, or preferably a CTL clone, that recognizes the housekeeping epitope can be used. In this case it is the target cell that expresses the embedded housekeeping epitope (instead of the pAPC during immunization) and it must express immune proteasome. Generally, the target cell can be transformed with an appropriate nucleic acid construct to confer expression of the embedded housekeeping epitope. Loading with a synthetic peptide embodying the embedded epitope using peptide loaded liposomes or a protein transfer reagent such as BIOPORTER™ (Gene Therapy Systems, San Diego, CA) represents an alternative.

Additional guidance on nucleic acid constructs useful as vaccines in accordance with the present invention are disclosed in U.S. Patent Application No. 09/561,572 entitled "EXPRESSION VECTORS ENCODING EPITOPES OF TARGET-ASSOCIATED ANTIGENS," filed on April 28, 2000. Further, expression vectors and methods for their design, which are useful in accordance with the present invention are disclosed in U.S. Patent Application No. 60/336,968 (attorney docket number CTLIMM.022PR) entitled "EXPRESSION VECTORS ENCODING EPITOPES OF TARGET-ASSOCIATED ANTIGENS AND METHODS FOR THEIR DESIGN," filed on 11/7/2001.

A preferred embodiment of the present invention includes a method of administering a vaccine including an epitope (or epitopes) to induce a therapeutic immune response. The vaccine is administered to a patient in a manner consistent with the standard vaccine delivery protocols that are known in the art. Methods of administering epitopes of TAAs including, without limitation, transdermal, intranodal, perinodal, oral, intravenous, intradermal, intramuscular, intraperitoneal, and mucosal administration, including delivery by injection, instillation or inhalation. A particularly useful method of vaccine delivery to elicit a CTL response is disclosed in Australian Patent No. 739189 issued January 17, 2002; U.S. Patent Application No. 09/380,534, filed on September 1, 1999; and a Continuation-in-Part thereof U.S. Patent Application No. 09/776,232 both entitled "A METHOD OF INDUCING A CTL RESPONSE," filed on February 2, 2001.

Reagents Recognizing Epitopes

In another aspect of the invention, proteins with binding specificity for the epitope and/or the epitope-MHC molecule complex are contemplated, as well as the isolated cells by which they can be expressed. In one set of embodiments these reagents take the form of immunoglobulins: polyclonal sera or monoclonal antibodies (mAb), methods for the generation of which are well know in the art. Generation of mAb with specificity for peptide-MHC molecule complexes is known in the art. See, for example, Aharoni et al. *Nature* 351:147-150, 1991; Andersen et al. *Proc. Natl. Acad. Sci. USA* 93:1820-1824, 1996; Dadaglio et al. *Immunity* 6:727-738, 1997; Duc et al. *Int. Immunol.* 5:427-431,1993; Eastman et al. *Eur. J. Immunol.* 26:385-393, 1996; Engberg et al. *Immunotechnology* 4:273-278, 1999; Porgdor et al. *Immunity* 6:715-726, 1997; Puri et al. *J. Immunol.* 158:2471-2476, 1997; and Polakova, K., et al. *J. Immunol.* 165 342-348, 2000.

In other embodiments the compositions can be used to induce and generate, *in vivo* and *in vitro*, T-cells specific for the any of the epitopes and/or epitope-MHC complexes. In preferred embodiments the epitope can be any one or more of those listed in TABLE 1, for example. Thus, embodiments also relate to and include isolated T cells, T cell clones, T cell hybridomas, or a protein containing the T cell receptor (TCR) binding domain derived from the cloned gene, as well as a recombinant cell expressing such a protein. Such TCR derived proteins can be simply the extra-cellular domains of the TCR, or a fusion with portions of another protein to confer a desired property or function. One example of such a fusion is the attachment of TCR binding domains to the constant regions of an antibody molecule so as to create a divalent molecule. The construction and activity of molecules following this general pattern have been reported, for example, Plaksin, D. et al. *J. Immunol.* 158:2218-2227, 1997 and Lebowitz, M.S. et al. *Cell Immunol.* 192:175-184, 1999. The more general construction and use of such molecules is also treated in U.S. patent 5,830,755 entitled T CELL RECEPTORS AND THEIR USE IN THERAPEUTIC AND DIAGNOSTIC METHODS.

The generation of such T cells can be readily accomplished by standard immunization of laboratory animals, and reactivity to human target cells can be obtained by immunizing with human target cells or by immunizing HLA-transgenic animals with the antigen/epitope. For some therapeutic approaches T cells derived from the same species are desirable. While such a cell can be created by cloning, for example, a murine TCR into a human T cell as contemplated above, *in vitro* immunization of human cells offers a potentially faster option. Techniques for *in vitro* immunization, even using naive donors, are know in the field, for example, Stauss et al., *Proc. Natl. Acad. Sci. USA* 89:7871-7875, 1992; Salgaller et al. *Cancer Res.* 55:4972-4979, 1995; Tsai et al., *J. Immunol.* 158:1796-1802, 1997; and Chung et al., *J. Immunother.* 22:279-287, 1999.

Any of these molecules can be conjugated to enzymes, radiochemicals, fluorescent tags, and toxins, so as to be used in the diagnosis (imaging or other detection), monitoring, and treatment of the pathogenic condition associated with the epitope. Thus a toxin conjugate can be administered to kill tumor cells, radiolabeling can facilitate imaging of epitope positive tumor, an enzyme conjugate can be used in an ELISA-like assay to diagnose cancer and confirm epitope expression in biopsied tissue. In a further embodiment, such T cells as set forth above, following expansion accomplished through stimulation with the epitope and/or cytokines, can be administered to a patient as an adoptive immunotherapy.

Reagents Comprising Epitopes

A further aspect of the invention provides isolated epitope-MHC complexes. In a particularly advantageous embodiment of this aspect of the invention, the complexes can be soluble, multimeric proteins such as those described in U. S. Patent No. 5,635,363 (tetramers) or U. S. Patent No. 6,015,884 (Ig-dimers). Such reagents are useful in detecting and monitoring specific T cell responses, and in purifying such T cells.

Isolated MHC molecules complexed with epitopic peptides can also be incorporated into planar lipid bilayers or liposomes. Such compositions can be used to stimulate T cells *in vitro* or, in the case of liposomes, *in vivo*. Co-stimulatory molecules (e.g. B7, CD40, LFA-3) can be incorporated into the same compositions or, especially for *in vitro* work, co-stimulation can be provided by anti-co-receptor antibodies (e.g. anti-CD28, anti-CD154, anti-CD2) or cytokines (e.g. IL-2, IL-12). Such stimulation of T cells can constitute vaccination, drive expansion of T cells *in vitro* for subsequent infusion in an immuotherapy, or constitute a step in an assay of T cell function.

The epitope, or more directly its complex with an MHC molecule, can be an important constituent of functional assays of antigen-specific T cells at either an activation or readout step or both. Of the many assays of T cell function current in the art (detailed procedures can be found in standard immunological references such as *Current Protocols in Immunology* 1999 John Wiley & Sons Inc., N.Y. two broad classes can be defined, those that measure the response of a pool of cells and those that measure the response of individual cells. Whereas the former conveys a global measure of the strength of a response, the latter allows determination of the relative frequency of responding cells. Examples of assays measuring global response are cytotoxicity assays, ELISA, and proliferation assays detecting cytokine secretion. Assays measuring the responses of individual cells (or small clones derived from them) include limiting dilution analysis (LDA), ELISPOT, flow cytometric detection of unsecreted cytokine (described in U.S. Patent No. 5,445,939, entitled "METHOD FOR ASSESSMENT OF THE MONONUCLEAR LEUKOCYTE IMMUNE SYSTEM" and U.S. Patent Nos 5,656,446; and 5,843,689, both entitled "METHOD

FOR THE ASSESSMENT OF THE MONONUCLEAR LEUKOCYTE IMMUNE SYSTEM," reagents for which are sold by Becton, Dickinson & Company under the tradename 'FASTIMMUNE' and detection of specific TCR with tetramers or Ig-dimers as stated and referenced above. The comparative virtues of these techniques have been reviewed in Yee, C. et al. *Current Opinion in Immunology*, 13:141–146, 2001. Additionally detection of a specific TCR rearrangement or expression can be accomplished through a variety of established nucleic acid based techniques, particularly in situ and single-cell PCR techniques, as will be apparent to one of skill in the art.

These functional assays are used to assess endogenous levels of immunity, response to an immunologic stimulus (e.g. a vaccine), and to monitor immune status through the course of a disease and treatment. Except when measuring endogenous levels of immunity, any of these assays presume a preliminary step of immunization, whether *in vivo* or *in vitro* depending on the nature of the issue being addressed. Such immunization can be carried out with the various embodiments of the invention described above or with other forms of immunogen (e.g., pAPC-tumor cell fusions) that can provoke similar immunity. With the exception of PCR and tetramer/Ig-dimer type analyses which can detect expression of the cognate TCR, these assays generally benefit from a step of *in vitro* antigenic stimulation which can advantageously use various embodiments of the invention as described above in order to detect the particular functional activity (highly cytolytic responses can sometimes be detected directly). Finally, detection of cytolytic activity requires epitope-displaying target cells, which can be generated using various embodiments of the invention. The particular embodiment chosen for any particular step depends on the question to be addressed, ease of use, cost, and the like, but the advantages of one embodiment over another for any particular set of circumstances will be apparent to one of skill in the art.

The peptide MHC complexes described in this section have traditionally been understood to be non-covalent associations. However it is possible, and can be advantageous, to create a covalent linkages, for example by encoding the epitope and MHC heavy chain or the epitope, ß2-microglobulin, and MHC heavy chain as a single protein (Yu, Y.L.Y., et al., J. Immunol. 168:3145-3149, 2002; Mottez, E., et at., *J. Exp. Med.* 181:493,1995; Dela Cruz, C. S., et al., *Int. Immunol.* 12:1293, 2000; Mage, M. G., et al., *Proc. Natl. Acad. Sci. USA* 89:10658,1992; Toshitani, K., et al., *Proc. Natl. Acad. Sci. USA* 93:236,1996; Lee, L., et al., *Eur. J. Immunol.* 24:2633,1994; Chung, D. H., et al., *J. Immunol.* 163:3699,1999; Uger, R. A. and B. H. Barber, J. Immunol. 160:1598, 1998; Uger, R. A., et al., *J. Immunol.* 162:6024,1999; and White, J., et al., *J. Immunol.* 162:2671, 1999. Such constructs can have superior stability and overcome roadblocks in

the processing- presentation pathway. They can be used in the already described vaccines, reagents, and assays in similar fashion.

Tumor Associated Antigens

Epitopes of the present invention are derived from the TuAAs tyrosinase (SEQ ID NO. 2), SSX-2, (SEQ ID NO. 3), PSMA (prostate-specific membrane antigen) (SEQ ID NO. 4), GP100, (SEQ ID NO. 70), MAGE-1, (SEQ ID NO. 71), MAGE-2, (SEQ ID NO. 72), MAGE-3, (SEQ ID NO. 73), NY-ESO-1, (SEQ ID NO. 74), PRAME, (SEQ ID NO. 77), PSA, (SEQ ID NO. 78), PSCA, (SEQ ID NO. 79), the ED-B domain of fibronectin (SEQ ID NOS 589 and 590), CEA (carcinoembryonic antigen) (SEQ ID NO. 592), Her2/Neu (SEQ ID NO. 594), SCP-1 (SEQ ID NO. 596) and SSX-4 (SEQ ID NO. 598). The natural coding sequences for these eleven proteins, or any segments within them, can be determined from their cDNA or complete coding (cds) sequences, SEQ ID NOS. 5-7, 80-87, 591, 593, 595, 597, and 599, respectively.

Tyrosinase is a melanin biosynthetic enzyme that is considered one of the most specific markers of melanocytic differentiation. Tyrosinase is expressed in few cell types, primarily in melanocytes, and high levels are often found in melanomas. The usefulness of tyrosinase as a TuAA is taught in U.S. Patent 5,747,271 entitled "METHOD FOR IDENTIFYING INDIVIDUALS SUFFERING FROM A CELLULAR ABNORMALITY SOME OF WHOSE ABNORMAL CELLS PRESENT COMPLEXES OF HLA-A2/TYROSINASE DERIVED PEPTIDES, AND METHODS FOR TREATING SAID INDIVIDUALS".

GP100, also known as PMel17, also is a melanin biosynthetic protein expressed at high levels in melanomas. GP100 as a TuAA is disclosed in U.S. Patent 5,844,075 entitled "MELANOMA ANTIGENS AND THEIR USE IN DIAGNOSTIC AND THERAPEUTIC METHODS,".

SSX-2, also know as Hom-Mel-40, is a member of a family of highly conserved cancer-testis antigens (Gure, A.O. et al. *Int. J. Cancer* 72:965-971, 1997. Its identification as a TuAA is taught in U.S. Patent 6,025,191 entitled "ISOLATED NUCLEIC ACID MOLECULES WHICH ENCODE A MELANOMA SPECIFIC ANTIGEN AND USES THEREOF,". Cancer-testis antigens are found in a variety of tumors, but are generally absent from normal adult tissues except testis. Expression of different members of the SSX family have been found variously in tumor cell lines. Due to the high degree of sequence identity among SSX family members, similar epitopes from more than one member of the family will be generated and able to bind to an MHC molecule, so that some vaccines directed against one member of this family can cross-react and be effective against other members of this family (see example 3 below).

MAGE-1, MAGE-2, and MAGE-3 are members of another family of cancer-testis antigens originally discovered in melanoma (MAGE is a contraction of melanoma-associated antigen) but

found in a variety of tumors. The identification of MAGE proteins as TuAAs is taught in U.S. Patent 5,342,774 entitled NUCLEOTIDE SEQUENCE ENCODING THE TUMOR REJECTION ANTIGEN PRECURSOR, MAGE-1, and in numerous subsequent patents. Currently there are 17 entries for (human) MAGE in the SWISS Protein database. There is extensive similarity among these proteins so in many cases, an epitope from one can induce a cross-reactive response to other members of the family. A few of these have not been observed in tumors, most notably MAGE-H1 and MAGE-D1, which are expressed in testes and brain, and bone marrow stromal cells, respectively. The possibility of cross-reactivity on normal tissue is ameliorated by the fact that they are among the least similar to the other MAGE proteins.

NY-ESO-1, is a cancer-testis antigen found in a wide variety of tumors, also known as CTAG-1 (Cancer-Testis Antigen-1) and CAG-3 (Cancer Antigen-3). NY-ESO-1 as a TuAA is disclosed in U.S. Patent 5,804,381 entitled ISOLATED NUCLEIC ACID MOLECULE ENCODING AN ESOPHAGEAL CANCER ASSOCIATED ANTIGEN, THE ANTIGEN ITSELF, AND USES THEREOF. A paralogous locus encoding antigens with extensive sequence identity, LAGE-1a/s (SEQ ID NO. 75) and LAGE-1b/L (SEQ ID NO. 76), have been disclosed in publicly available assemblies of the human genome , and have been concluded to arise through alternate splicing. Additionally, CT-2 (or CTAG-2, Cancer-Testis Antigen-2) appears to be either an allele, a mutant, or a sequencing discrepancy of LAGE-1b/L. Due to the extensive sequence identity, many epitopes from NY-ESO-1 can also induce immunity to tumors expressing these other antigens. See figure 1. The proteins are virtually identical through amino acid 70. From 71-134 the longest run of identities between NY-ESO-1 and LAGE is 6 residues, but potentially cross-reactive sequences are present. And from 135-180 NY-ESO and LAGE-1a/s are identical except for a single residue, but LAGE-1b/L is unrelated due to the alternate splice. The CAMEL and LAGE-2 antigens appear to derive from the LAGE-1 mRNA, but from alternate reading frames, thus giving rise to unrelated protein sequences. More recently, GenBank Accession AF277315.5, Homo sapiens chromosome X clone RP5-865E18, RP5-1087L19, complete sequence, reports three independent loci in this region which are labeled as LAGE1 (corresponding to CTAG-2 in the genome assemblies), plus LAGE2-A and LAGE2-B (both corresponding to CTAG-1 in the genome assemblies).

PSMA (prostate-specific membranes antigen), a TuAA described in U.S. Patent 5,538,866 entitled "PROSTATE-SPECIFIC MEMBRANES ANTIGEN", is expressed by normal prostate epithelium and, at a higher level, in prostatic cancer. It has also been found in the neovasculature of non-prostatic tumors. PSMA can thus form the basis for vaccines directed to both prostate cancer and to the neovasculature of other tumors. This later concept is more fully described in a provisional U.S. Patent application No. 60/274,063 entitled ANTI-NEOVASCULAR VACCINES

FOR CANCER, filed March 7, 2001, and U.S. Application No. 10/094,699, attorney docket number CTLIMM.015A, filed on March 7, 2002, entitled "ANTI-NEOVASCULAR PREPARATIONS FOR CANCER,". Briefly, as tumors grow they recruit ingrowth of new blood vessels. This is understood to be necessary to sustain growth as the centers of unvascularized tumors are generally necrotic and angiogenesis inhibitors have been reported to cause tumor regression. Such new blood vessels, or neovasculature, express antigens not found in established vessels, and thus can be specifically targeted. By inducing CTL against neovascular antigens the vessels can be disrupted, interrupting the flow of nutrients to (and removal of wastes from) tumors, leading to regression.

Alternate splicing of the PSMA mRNA also leads to a protein with an apparent start at Met_{58}, thereby deleting the putative membrane anchor region of PSMA as described in U.S. Patent 5,935,818 entitled "ISOLATED NUCLEIC ACID MOLECULE ENCODING ALTERNATIVELY SPLICED PROSTATE-SPECIFIC MEMBRANES ANTIGEN AND USES THEREOF". A protein termed PSMA-like protein, Genbank accession number AF261715, is nearly identical to amino acids 309-750 of PSMA and has a different expression profile. Thus the most preferred epitopes are those with an N-terminus located from amino acid 58 to 308.

PRAME, also know as MAPE, DAGE, and OIP4, was originally observed as a melanoma antigen. Subsequently, it has been recognized as a CT antigen, but unlike many CT antigens (e.g., MAGE, GAGE, and BAGE) it is expressed in acute myeloid leukemias. PRAME is a member of the MAPE family which consists largely of hypothetical proteins with which it shares limited sequence similarity. The usefulness of PRAME as a TuAA is taught in U.S. Patent 5,830,753 entitled "ISOLATED NUCLEIC ACID MOLECULES CODING FOR TUMOR REJECTION ANTIGEN PRECURSOR DAGE AND USES THEREOF".

PSA, prostate specific antigen, is a peptidase of the kallikrein family and a differentiation antigen of the prostate. Expression in breast tissue has also been reported. Alternate names include gamma-seminoprotein, kallikrein 3, seminogelase, seminin, and P-30 antigen. PSA has a high degree of sequence identity with the various alternate splicing products prostatic/glandular kallikrein-1 and –2, as well as kalikrein 4, which is also expressed in prostate and breast tissue. Other kallikreins generally share less sequence identity and have different expression profiles. Nonetheless, cross-reactivity that might be provoked by any particular epitope, along with the likelihood that that epitope would be liberated by processing in non-target tissues (most generally by the housekeeping proteasome), should be considered in designing a vaccine.

PSCA, prostate stem cell antigen, and also known as SCAH-2, is a differentiation antigen preferentially expressed in prostate epithelial cells, and overexpresssed in prostate cancers. Lower level expression is seen in some normal tissues including neuroendocrine cells of the digestive

tract and collecting ducts of the kidney. PSCA is described in U.S. Patent 5,856,136 entitled "HUMAN STEM CELL ANTIGENS".

Synaptonemal complex protein 1 (SCP-1), also known as HOM-TES-14, is a meiosis-associated protein and also a cancer-testis antigen (Tureci, O., et al. Proc. Natl. Acad. Sci. USA 95:5211-5216, 1998). As a cancer antigen its expression is not cell-cycle regulated and it is found frequently in gliomas, breast, renal cell, and ovarian carcinomas. It has some similarity to myosins, but with few enough identities that cross-reactive epitopes are not an immediate prospect.

The ED-B domain of fibronectin is also a potential target. Fibronectin is subject to developmentally regulated alternative splicing, with the ED-B domain being encoded by a single exon that is used primarily in oncofetal tissues (Matsuura, H. and S. Hakomori *Proc. Natl. Acad. Sci. USA* 82:6517-6521, 1985; Carnemolla, B. et al. *J. Cell Biol.* 108:1139-1148, 1989; Loridon-Rosa, B. et al. *Cancer Res.*50:1608-1612, 1990; Nicolo, G. et al. *Cell Differ. Dev.* 32:401-408, 1990; Borsi, L. et al. *Exp. Cell Res.* 199:98-105, 1992; Oyama, F. et al. *Cancer Res.* 53:2005-2011, 1993; Mandel, U. et al. *APMIS* 102:695-702, 1994; Farnoud, M.R. et al. *Int. J. Cancer* 61:27-34, 1995; Pujuguet, P. et al. Am. J. Pathol. 148:579-592, 1996; Gabler, U. et al. *Heart* 75:358-362, 1996;Chevalier, X. *Br. J. Rheumatol.* 35:407-415, 1996; Midulla, M. *Cancer Res.* 60:164-169, 2000).

The ED-B domain is also expressed in fibronectin of the neovasculature (Kaczmarek, J. et al. *Int. J. Cancer* 59:11-16, 1994; Castellani, P. et al. *Int. J. Cancer* 59:612-618, 1994; Neri, D. et al. *Nat. Biotech.* 15:1271-1275, 1997; Karelina, T.V. and A.Z. Eisen *Cancer Detect. Prev.* 22:438-444, 1998; Tarli, L. et al. *Blood* 94:192-198; 1999; Castellani, P. et al. *Acta Neurochir. (Wien)* 142:277-282, 2000). As an oncofetal domain, the ED-B domain is commonly found in the fibronectin expressed by neoplastic cells in addition to being expressed by the neovasculature. Thus, CTL-inducing vaccines targeting the ED-B domain can exhibit two mechanisms of action: direct lysis of tumor cells, and disruption of the tumor's blood supply through destruction of the tumor-associated neovasculature. As CTL activity can decay rapidly after withdrawal of vaccine, interference with normal angiogenesis can be minimal. The design and testing of vaccines targeted to neovasculature is described in Provisional U.S. Patent Application No. 60/274,063 entitled "ANTI-NEOVASCULATURE VACCINES FOR CANCER" and in U.S. Patent Application No. 10/094,699, attorney docket number CTLIMM.015A, entitled "ANTI-NEOVASCULATURE PREPARATIONS FOR CANCER, filed on date even with this application (March 7, 2002). A tumor cell line is disclosed in Provisional U.S. Application No. 60/363,131, filed on March 7, 2002, attorney docket number CTLIMM.028PR, entitled "HLA-TRANSGENIC MURINE TUMOR CELL LINE,".

Carcinoembryonic antigen (CEA) is a paradigmatic oncofetal protein first described in 1965 (Gold and Freedman, J. Exp. Med. 121: 439-462, 1965. Fuller references can be found in the Online Medelian Inheritance in Man; record *114890). It has officially been renamed carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5). Its expression is most strongly associated with adenocarcinomas of the epithelial lining of the digestive tract and in fetal colon. CEA is a member of the immunoglobulin supergene family and the defining member of the CEA subfamily.

HER2/NEU is an oncogene related to the epidermal growth factor receptor (van de Vijver, et al., *New Eng. J. Med.* 319:1239-1245, 1988), and apparently identical to the c-ERBB2 oncogene (Di Fiore, et al., Science 237: 178-182, 1987). The over-expression of ERBB2 has been implicated in the neoplastic transformation of prostate cancer. As HER2 it is amplified and over-expressed in 25-30% of breast cancers among other tumors where expression level is correlated with the aggressiveness of the tumor (Slamon, et al., *New Eng. J. Med.* 344:783-792, 2001). A more detailed description is available in the Online Medelian Inheritance in Man; record *164870.

Additional disclosure related to embodiments of the present invention is found in U.S. Patent Application No. 10/005,905 (attorney docket number CTLIMM.021CP1) entitled "EPITOPE SYNCHRONIZATION IN ANTIGEN PRESENTING CELLS," filed on November 7, 2001 and a continuation thereof, U.S. Application No. __/_____, filed on December 7, 2000, attorney docket number CTLIMM.21CP1C, also entitled "EPITOPE SYNCHRONIZATION IN ANTIGEN PRESENTING CELLS."

Useful epitopes were identified and tested as described in the following examples. However, these examples are intended for illustration purposes only, and should not be construed as limiting the scope of the invention in any way.

EXAMPLES

Sequences of Specific Preferred Epitopes

Example 1

Manufacture of epitopes.

A. Synthetic production of epitopes

Peptides having an amino acid sequence of any of SEQ ID NO: 1, 8, 9, 11-23, 26-29, 32-44, 47-54, 56-63, 66-68 88-253, or 256-588 are synthesized using either FMOC or tBOC solid phase synthesis methodologies. After synthesis, the peptides are cleaved from their supports with either trifluoroacetic acid or hydrogen fluoride, respectively, in the presence of appropriate protective scavengers. After removing the acid by evaporation, the peptides are extracted with ether to remove the scavengers and the crude, precipitated peptide is then lyophilized. Purity of

the crude peptides is determined by HPLC, sequence analysis, amino acid analysis, counterion content analysis and other suitable means. If the crude peptides are pure enough (greater than or equal to about 90% pure), they can be used as is. If purification is required to meet drug substance specifications, the peptides are purified using one or a combination of the following: re-precipitation; reverse-phase, ion exchange, size exclusion or hydrophobic interaction chromatography; or counter-current distribution.

Drug product formulation

GMP-grade peptides are formulated in a parenterally acceptable aqueous, organic, or aqueous-organic buffer or solvent system in which they remain both physically and chemically stable and biologically potent. Generally, buffers or combinations of buffers or combinations of buffers and organic solvents are appropriate. The pH range is typically between 6 and 9. Organic modifiers or other excipients can be added to help solubilize and stabilize the peptides. These include detergents, lipids, co-solvents, antioxidants, chelators and reducing agents. In the case of a lyophilized product, sucrose or mannitol or other lyophilization aids can be added. Peptide solutions are sterilized by membrane filtration into their final container-closure system and either lyophilized for dissolution in the clinic, or stored until use.

B. Construction of expression vectors for use as nucleic acid vaccines

The construction of three generic epitope expression vectors is presented below. The particular advantages of these designs are set forth in U.S. Patent Application No. 09/561,572 entitled "EXPRESSION VECTORS ENCODING EPITOPES OF TARGET-ASSOCIATED ANTIGENS,".

A suitable *E. coli* strain was then transfected with the plasmid and plated out onto a selective medium. Several colonies were grown up in suspension culture and positive clones were identified by restriction mapping. The positive clone was then grown up and aliquotted into storage vials and stored at -70°C.

A mini-prep (QIAprep Spin Mini-prep: Qiagen, Valencia, CA) of the plasmid was then made from a sample of these cells and automated fluorescent dideoxy sequence analysis was used to confirm that the construct had the desired sequence.

B.1 Construction of pVAX-EP1-IRES-EP2

Overview:

The starting plasmid for this construct is pVAX1 purchased from Invitrogen (Carlsbad, CA). Epitopes EP1 and EP2 were synthesized by GIBCO BRL (Rockville, MD). The IRES was excised from pIRES purchased from Clontech (Palo Alto, CA).

Procedure:

1 pIRES was digested with EcoRI and NotI. The digested fragments were separated by agarose gel electrophoresis, and the IRES fragment was purified from the excised band.

2 pVAX1 was digested with EcoRI and NotI, and the pVAX1 fragment was gel-purified.

3 The purified pVAX1 and IRES fragments were then ligated together.

4 Competent E. coli of strain DH5α were transformed with the ligation mixture.

5 Minipreps were made from 4 of the resultant colonies.

6 Restriction enzyme digestion analysis was performed on the miniprep DNA. One recombinant colony having the IRES insert was used for further insertion of EP1 and EP2. This intermediate construct was called pVAX-IRES.

7 Oligonucleotides encoding EP1 and EP2 were synthesized.

8 EP1 was subcloned into pVAX-IRES between AflII and EcoRI sites, to make pVAX-EP1-IRES;

9 EP2 was subcloned into pVAX-EP1-IRES between SalI and NotI sites, to make the final construct pVAX-EP1-IRES-EP2.

10 The sequence of the EP1-IRES-EP2 insert was confirmed by DNA sequencing.

B 2. Construction of pVAX-EP1-IRES-EP2-ISS-NIS

Overview:

The starting plasmid for this construct was pVAX-EP1-IRES-EP2 (Example 1). The ISS (immunostimulatory sequence) introduced into this construct is AACGTT, and the NIS (standing for nuclear import sequence) used is the SV40 72bp repeat sequence. ISS-NIS was synthesized by GIBCO BRL. See Figure 2.

Procedure:

1 pVAX-EP1-IRES-EP2 was digested with NruI; the linearized plasmid was gel-purified.

2 ISS-NIS oligonucleotide was synthesized.

3 The purified linearized pVAX-EP1-IRES-EP2 and synthesized ISS-NIS were ligated together.

4 Competent E. coli of strain DH5α were transformed with the ligation product.

5 Minipreps were made from resultant colonies.

6 Restriction enzyme digestions of the minipreps were carried out.

7 The plasmid with the insert was sequenced.

B3. Construction of pVAX-EP2-UB-EP1

Overview:

The starting plasmid for this construct was pVAX1 (Invitrogen). EP2 and EP1 were synthesized by GIBCO BRL. Wild type Ubiquitin cDNA encoding the 76 amino acids in the construct was cloned from yeast.

Procedure:

1 RT-PCR was performed using yeast mRNA. Primers were designed to amplify the complete coding sequence of yeast Ubiquitin.

2 The RT-PCR products were analyzed using agarose gel electrophoresis. A band with the predicted size was gel-purified.

3 The purified DNA band was subcloned into pZERO1 at EcoRV site. The resulting clone was named pZERO-UB.

4 Several clones of pZERO-UB were sequenced to confirm the Ubiquitin sequence before further manipulations.

5 EP1 and EP2 were synthesized.

6 EP2, Ubiquitin and EP1 were ligated and the insert cloned into pVAX1 between BamHI and EcoRI, putting it under control of the CMV promoter.

7 The sequence of the insert EP2-UB-EP1 was confirmed by DNA sequencing.

Example 2

Identification of useful epitope variants.

The 10-mer FLPWHRLFLL (SEQ ID NO. 1) is identified as a useful epitope. Based on this sequence, numerous variants are made. Variants exhibiting activity in HLA binding assays (see Example 3, section 6) are identified as useful, and are subsequently incorporated into vaccines.

The HLA-A2 binding of length variants of FLPWHRLFLL have been evaluated. Proteasomal digestion analysis indicates that the C-terminus of the 9-mer FLPWHRLFL (SEQ ID NO. 8) is also produced. Additionally the 9-mer LPWHRLFLL (SEQ ID NO. 9) can result from N-terminal trimming of the 10-mer. Both are predicted to bind to the HLA-A*0201 molecule, however of these two 9-mers, FLPWHRLFL displayed more significant binding and is preferred (see Figs. 3A and B).

In vitro proteasome digestion and N-terminal pool sequencing indicates that tyrosinase$_{207-216}$ (SEQ ID NO. 1) is produced more commonly than tyrosinase$_{207-215}$ (SEQ ID NO. 8), however the latter peptide displays superior immunogenicity, a potential concern in arriving at an optimal vaccine design. FLPWHRLFL, tyrosinase$_{207-215}$ (SEQ ID NO. 8) was used in an in vitro immunization of HLA-A2$^+$ blood to generate CTL (see CTL Induction Cultures below). Using

peptide pulsed T2 cells as targets in a standard chromium release assay it was found that the CTL induced by tyrosinase$_{207-215}$ (SEQ ID NO. 8) recognize tyrosinase$_{207-216}$ (SEQ ID NO. 1) targets equally well (see fig. 3C). These CTL also recognize the HLA-A2$^+$, tyrosinase$^+$ tumor cell lines 624.38 and HTB64, but not 624.28 an HLA-A2$^-$ derivative of 624.38 (fig. 3C). Thus the relative amounts of these two epitopes produced in vivo, does not become a concern in vaccine design.

CTL induction cultures

PBMCs from normal donors were purified by centrifugation in Ficoll-Hypaque from buffy coats. All cultures were carried out using the autologous plasma (AP) to avoid exposure to potential xenogeneic pathogens and recognition of FBS peptides. To favor the in vitro generation of peptide-specific CTL, we employed autologous dendritic cells (DC) as APCs. DC were generated and CTL were induced with DC and peptide from PBMCs as described (Keogh et al., 2001). Briefly, monocyte-enriched cell fractions were cultured for 5 days with GM-CSF and IL-4 and were cultured for 2 additional days in culture media with 2 μg/ml CD40 ligand to induce maturation. 2 x10^6 CD8+-enriched T lymphocytes/well and 2 x10^5 peptide-pulsed DC/well were co-cultured in 24-well plates in 2 ml RPMI supplemented with 10% AP, 10 ng/ml IL-7 and 20 IU/ml IL-2. Cultures were restimulated on days 7 and 14 with autologous irradiated peptide-pulsed DC.

Sequence variants of FLPWHRLFL are constructed as follow. Consistent with the binding coefficient table (see Table 3) from the NIH/BIMAS MHC binding prediction program (see reference in example 3 below), binding can be improved by changing the L at position 9, an anchor position, to V. Binding can also be altered, though generally to a lesser extent, by changes at non-anchor positions. Referring generally to Table 3, binding can be increased by employing residues with relatively larger coefficients. Changes in sequence can also alter immunogenicity independently of their effect on binding to MHC. Thus binding and/or immunogenicity can be improved as follows:

By substituting F,L,M,W, or Y for P at position 3; these are all bulkier residues that can also improve immunogenicity independent of the effect on binding. The amine and hydroxyl-bearing residues, Q and N; and S and T; respectively, can also provoke a stronger, cross-reactive response.

By substituting D or E for W at position 4 to improve binding; this addition of a negative charge can also make the epitope more immunogenic, while in some cases reducing cross-reactivity with the natural epitope. Alternatively the conservative substitutions of F or Y can provoke a cross-reactive response.

By substituting F for H at position 5 to improve binding. H can be viewed as partially charged, thus in some cases the loss of charge can hinder cross-reactivity. Substitution of the fully

charged residues R or K at this position can enhance immunogenicity without disrupting charge-dependent cross-reactivity.

By substituting I, L, M, V, F, W, or Y for R at position 6. The same caveats and alternatives apply here as at position 5.

By substituting W or F for L at position 7 to improve binding. Substitution of V, I, S, T, Q, or N at this position are not generally predicted to reduce binding affinity by this model (the NIH algorithm), yet can be advantageous as discussed above.

Y and W, which are equally preferred as the Fs at positions 1 and 8, can provoke a useful cross-reactivity. Finally, while substitutions in the direction of bulkiness are generally favored to improve immunogenicity, the substitution of smaller residues such as A, S, and C, at positions 3-7 can be useful according to the theory that contrast in size, rather than bulkiness per se, is an important factor in immunogenicity. The reactivity of the thiol group in C can introduce other properties as discussed in Chen, J.-L., et al. *J. Immunol.* 165:948-955, 2000.

Table 3. 9-mer Coefficient Table for HLA-A*0201*

HLA Coefficient table for file "A_0201_standard"									
Amino Acid Type	1st	2nd	3rd	4th	5th	6th	7th	8th	9th
A	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
C	1.000	0.470	1.000	1.000	1.000	1.000	1.000	1.000	1.000
D	0.075	0.100	0.400	4.100	1.000	1.000	0.490	1.000	0.003
E	0.075	1.400	0.064	4.100	1.000	1.000	0.490	1.000	0.003
F	4.600	0.050	3.700	1.000	3.800	1.900	5.800	5.500	0.015
G	1.000	0.470	1.000	1.000	1.000	1.000	0.130	1.000	0.015
H	0.034	0.050	1.000	1.000	1.000	1.000	1.000	1.000	0.015
I	1.700	9.900	1.000	1.000	1.000	2.300	1.000	0.410	2.100
K	3.500	0.100	0.035	1.000	1.000	1.000	1.000	1.000	0.003
L	1.700	72.000	3.700	1.000	1.000	2.300	1.000	1.000	4.300
M	1.700	52.000	3.700	1.000	1.000	2.300	1.000	1.000	1.000
N	1.000	0.470	1.000	1.000	1.000	1.000	1.000	1.000	0.015
P	0.022	0.470	1.000	1.000	1.000	1.000	1.000	1.000	0.003
Q	1.000	7.300	1.000	1.000	1.000	1.000	1.000	1.000	0.003
R	1.000	0.010	0.076	1.000	1.000	1.000	0.200	1.000	0.003
S	1.000	0.470	1.000	1.000	1.000	1.000	1.000	1.000	0.015
T	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.500
V	1.700	6.300	1.000	1.000	1.000	2.300	1.000	0.410	14.000
W	4.600	0.010	8.300	1.000	1.000	1.700	7.500	5.500	0.015
Y	4.600	0.010	3.200	1.000	1.000	1.500	1.000	5.500	0.015

*This table and other comparable data that are publicly available are useful in designing epitope variants and in determining whether a particular variant is substantially similar, or is functionally similar.

Example 3

Cluster Analysis (SSX-2_{31-68}).

1. Epitope cluster region prediction:

The computer algorithms: SYFPEITHI (internet http:// access at syfpeithi.bmi-heidelberg.com/Scripts/MHCServer.dll/EpPredict.htm), based on the book "MHC Ligands and Peptide Motifs" by H.G.Rammensee, J.Bachmann and S.Stevanovic; and HLA Peptide Binding Predictions (NIH) (internet http:// access at bimas.dcrt.nih.gov/molbio/hla_bin), described in Parker, K. C., et al., *J. Immunol.* 152:163, 1994; were used to analyze the protein sequence of SSX-2 (GI:10337583). Epitope clusters (regions with higher than average density of peptide fragments with high predicted MHC affinity) were defined as described fully in U.S. Patent Application No. 09/561,571 entitled "EPITOPE CLUSTERS," filed on April 28, 2000. Using a epitope density ratio cutoff of 2, five and two clusters were defined using the SYFPETHI and NIH algorithms, respectively, and peptides score cutoffs of 16 (SYFPETHI) and 5 (NIH). The highest

scoring peptide with the NIH algorithm, SSX-2_{41-49}, with an estimated halftime of dissociation of >1000 min., does not overlap any other predicted epitope but does cluster with SSX-2_{57-65} in the NIH analysis.

2. Peptide synthesis and characterization:

SSX-2_{31-68}, YFSKEEWEKMKASEKIFYVYMKRKYEAMTKLGFKATLP (SEQ ID NO. 10) was synthesized by MPS (Multiple Peptide Systems, San Diego, CA 92121) using standard solid phase chemistry. According to the provided 'Certificate of Analysis', the purity of this peptide was 95%.

3. Proteasome digestion:

Proteasome was isolated from human red blood cells using the proteasome isolation protocol described in U.S. Patent Application No. 09/561,074 entitled "METHOD OF EPITOPE DISCOVERY," filed on April 28, 2000. SDS-PAGE, western-blotting, and ELISA were used as quality control assays. The final concentration of proteasome was 4 mg/ml, which was determined by non-interfering protein assay (Geno Technologies Inc.). Proteasomes were stored at -70°C in 25 µl aliquots.

SSX-2_{31-68} was dissolved in Milli-Q water, and a 2 mM stock solution prepared and 20µL aliquots stored at -20°C.

1 tube of proteasome (25 µL) was removed from storage at-70°C and thawed on ice. It was then mixed thoroughly with 12.5µL of 2mM peptide by repipetting (samples were kept on ice). A 5µL sample was immediately removed after mixing and transferred to a tube containing 1.25µL 10%TFA (final concentration of TFA was 2%); the T=0 min sample. The proteasome digestion reaction was then started and carried out at 37°C in a programmable thermal controller. Additional 5µL samples were taken out at 15, 30, 60, 120, 180 and 240 min respectively, the reaction was stopped by adding the sample to 1.25µL 10% TFA as before. Samples were kept on ice or frozen until being analyzed by MALDI-MS. All samples were saved and stored at –20°C for HPLC analysis and N-terminal sequencing. Peptide alone (without proteasome) was used as a blank control: 2 µL peptide + 4µL Tris buffer (20 mM, pH 7.6) + 1.5µL TFA.

4. MALDI-TOF MS measurements:

For each time point 0.3 µL of matrix solution (10mg/ml α-cyano-4-hydroxycinnamic acid in AcCN/H_2O (70:30)) was first applied on a sample slide, and then an equal volume of digested sample was mixed gently with matrix solution on the slide. The slide was allowed to dry at ambient air for 3-5 min. before acquiring the mass spectra. MS was performed on a Lasermat 2000 MALDI-TOF mass spectrometer that was calibrated with peptide/protein standards. To improve the accuracy of measurement, the molecular ion weight (MH^+) of the peptide substrate was used as

an internal calibration standard. The mass spectrum of the T=120 min. digested sample is shown in figure 4.

5. MS data analysis and epitope identification:

To assign the measured mass peaks, the computer program MS-Product, a tool from the UCSF Mass Spectrometry Facility (http:// accessible at prospector.ucsf.edu/ucsfhtml3.4/msprod.htm), was used to generate all possible fragments (N- and C-terminal ions, and internal fragments) and their corresponding molecular weights. Due to the sensitivity of the mass spectrometer, average molecular weight was used. The mass peaks observed over the course of the digestion were identified as summarized in Table 4.

Fragments co-C-terminal with 8-10 amino acid long sequences predicted to bind HLA by the SYFPEITHI or NIH algorithms were chosen for further study. The digestion and prediction steps of the procedure can be usefully practiced in any order. Although the substrate peptide used in proteasomal digest described here was specifically designed to include predicted HLA-A2.1 binding sequences, the actual products of digestion can be checked after the fact for actual or predicted binding to other MHC molecules. Selected results are shown in Table 5.

Table 4. SSX-2_{31-68} Mass Peak Identification.

MS PEAK (measured)	PEPTIDE	SEQUENCE	CALCULATED MASS (MH^+)
988.23	31-37	YFSKEEW	989.08
1377.68±2.38	31-40	YFSKEEWEKM	1377.68
1662.45±1.30	31-43	YFSKEEWEKMKAS	1663.90
2181.72±0.85	31-47	YFSKEEWEKMKASEKIF	2181.52
2346.6	31-48	YFSKEEWEKMKASEKIFY	2344.71
1472.16±1.54	38-49	EKMKASEKIFYV	1473.77
2445.78±1.18	31-49*	YFSKEEWEKMKASEKIFYV	2443.84
2607.	31-50	YFSKEEWEKMKASEKIFYVY	2607.02
1563.3	50-61	YMKRKYEAMTKL	1562.93
3989.9	31-61	YFSKEEWEKMKASEKIFYVYMKRKYEAMTKL	3987.77
1603.74±1.5	51-63		1603.98

3		MKRKYEAMTKLGF	
1766.45±1.5	50-63	YMKRKYEAMTKLGF	1767.16
1866.32±1.2 2	49-63	VYMKRKYEAMTKLGF	1866.29
4192.6	31-63	YFSKEEWEKMKASEKIFYVYMKRKYEAMTKLG F	4192.00
4392.1	31-65**	YFSKEEWEKMKASEKIFYVYMKRKYEAMTKLG FKA	4391.25

Boldface sequence correspond to peptides predicted to bind to MHC.

* On the basis of mass alone this peak could also have been assigned to the peptide 32-50, however proteasomal removal of just the N-terminal amino acid is unlikely. N-terminal sequencing (below) verifies the assignment to 31-49.

** On the basis of mass this fragment might also represent 33-68. N-terminal sequencing below is consistent with the assignment to 31-65.

Table 5. Predicted HLA binding by proteasomally generated fragments

SEQ ID NO.	PEPTIDE	HLA	SYFPEITHI	NIH
11	FSKEEWEKM	B*3501	NP†	90
12	KMKASEKIF	B*08	17	<5
13 & (14)	(K)MKASEKIFY	A1	19 (19)	<5
15 &(16)	(M)KASEKIFYV	A*0201	22 (16)	1017
		B*08	17	<5
		B*5101	22 (13)	60
		B*5102	NP	133
		B*5103	NP	121
17 & (18)	(K)ASEKIFYVY	A1	34 (19)	14
19 & (20)	(K)RKYEAMTKL	A*0201	15	<5
		A26	15	NP
		B14	NP	45 (60)
		B*2705	21	15
		B*2709	16	NP
		B*5101	15	<5
21	KYEAMTKLGF	A1	16	<5
		A24	NP	300
22	YEAMTKLGF	B*4403	NP	80
23	EAMTKLGF	B*08	22	<5

†No prediction

As seen in Table 5, N-terminal addition of authentic sequence to epitopes can generate epitopes for the same or different MHC restriction elements. Note in particular the pairing of (K)RKYEAMTKL (SEQ ID NOS 19 and (20)) with HLA-B14, where the 10-mer has a longer predicted halftime of dissociation than the co-C-terminal 9-mer. Also note the case of the 10-mer KYEAMTKLGF (SEQ ID NO. 21) which can be used as a vaccine useful with several MHC types by relying on N-terminal trimming to create the epitopes for HLA-B*4403 and –B*08.

6. HLA-A0201 binding assay:

Binding of the candidate epitope KASEKIFYV, SSX-2_{41-49}, (SEQ ID NO. 15) to HLA-A2.1 was assayed using a modification of the method of Stauss et al., (Proc Natl Acad Sci USA 89(17):7871-5 (1992)). Specifically, T2 cells, which express empty or unstable MHC molecules on their surface, were washed twice with Iscove's modified Dulbecco's medium (IMDM) and cultured overnight in serum-free AIM-V medium (Life Technologies, Inc., Rockville, MD) supplemented with human ß2-microglobulin at 3µg/ml (Sigma, St. Louis, MO) and added peptide, at 800, 400, 200, 100, 50, 25, 12.5, and 6.25 µg/ml.in a 96-well flat-bottom plate at $3x10^5$ cells/200 µl/well. Peptide was mixed with the cells by repipeting before distributing to the plate (alternatively peptide can be added to individual wells), and the plate was rocked gently for 2 minutes. Incubation was in a 5% CO_2 incubator at 37°C. The next day the unbound peptide was removed by washing twice with serum free RPMI medium and a saturating amount of anti-class I HLA monoclonal antibody, fluorescein isothiocyanate (FITC)-conjugated anti-HLA A2, A28 (One Lambda, Canoga Park, CA) was added. After incubation for 30 minutes at 4°C, cells were washed 3 times with PBS supplemented with 0.5% BSA, 0.05%(w/v) sodium azide, pH 7.4-7.6 (staining buffer). (Alternatively W6/32 (Sigma) can be used as the anti-class I HLA monoclonal antibody the cells washed with staining buffer and then incubated with fluorescein isothiocyanate (FITC)-conjugated goat F(ab') antimouse-IgG (Sigma) for 30 min at 4°C and washed 3 times as before.) The cells were resuspended in 0.5 ml staining buffer. The analysis of surface HLA-A2.1 molecules stabilized by peptide binding was performed by flow cytometry using a FACScan (Becton Dickinson, San Jose, CA). If flow cytometry is not to be performed immediately the cells can be fixed by adding a quarter volume of 2% paraformaldehyde and storing in the dark at 4 C.

The results of the experiment are shown in Figure 5. SSX-2_{41-49} (SEQ ID NO. 15) was found to bind HLA-A2.1 to a similar extent as the known A2.1 binder FLPSDYFPSV (HBV_{18-27}; SEQ ID NO: 24) used as a positive control. An HLA-B44 binding peptide, AEMGKYSFY (SEQ ID NO: 25), was used as a negative control. The fluoresence obtained from the negative control was similar to the signal obtained when no peptide was used in the assay. Positive and negative

control peptides were chosen from Table 18.3.1 in *Current Protocols in Immunology* p. 18.3.2, John Wiley and Sons, New York, 1998.

7. Immunogenicity:

A. *In vivo* immunization of mice.

HHD1 transgenic A*0201 mice (Pascolo, S., et al. *J. Exp. Med.* 185:2043-2051, 1997) were anesthetized and injected subcutaneously at the base of the tail, avoiding lateral tail veins, using 100 µl containing 100 nmol of SSX-2_{41-49} (SEQ ID NO. 15) and 20 µg of HTL epitope peptide in PBS emulsified with 50 µl of IFA (incomplete Freund's adjuvant).

B. Preparation of stimulating cells (LPS blasts).

Using spleens from 2 naive mice for each group of immunized mice, un-immunized mice were sacrificed and the carcasses were placed in alcohol. Using sterile instruments, the top dermal layer of skin on the mouse's left side (lower mid-section) was cut through, exposing the peritoneum. The peritoneum was saturated with alcohol, and the spleen was aseptically extracted. The spleen was placed in a petri dish with serum-free media. Splenocytes were isolated by using sterile plungers from 3 ml syringes to mash the spleens. Cells were collected in a 50 ml conical tubes in serum-free media, rinsing dish well. Cells were centrifuged (12000 rpm, 7 min) and washed one time with RPMI. Fresh spleen cells were resuspended to a concentration of $1x10^6$ cells per ml in RPMI-10%FCS (fetal calf serum). 25g/ml lipopolysaccharide and 7 µg/ml Dextran Sulfate were added. Cell were incubated for 3 days in T-75 flasks at 37°C, with 5% CO_2. Splenic blasts were collected in 50 ml tubes pelleted (12000 rpm, 7 min) and resuspended to $3X10^{7}$/ml in RPMI. The blasts were pulsed with the priming peptide at 50 µg/ml, RT 4hr. mitomycin C-treated at 25µg/ml, 37^0C, 20 min and washed three times with DMEM.

C. *In vitro* stimulation.

3 days after LPS stimulation of the blast cells and the same day as peptide loading, the primed mice were sacrificed (at 14 days post immunization) to remove spleens as above. $3x10^6$ splenocytes were co-cultured with $1x10^6$ LPS blasts/well in 24-well plates at 37°C, with 5% CO_2 in DMEM media supplemented with 10% FCS, $5x10^{-5}$ M β-mercaptoethanol, 100µg/ml streptomycin and 100 IU/ml penicillin. Cultures were fed 5% (vol/vol) ConA supernatant on day 3 and assayed for cytolytic activity on day 7 in a ^{51}Cr-release assay.

D. Chromium-release assay measuring CTL activity.

To assess peptide specific lysis, $2x10^6$ T2 cells were incubated with 100 µCi sodium chromate together with 50 µg/ml peptide at 37 C for 1 hour. During incubation they were gently shaken every 15 minutes. After labeling and loading, cells were washed three times with 10 ml of DMEM-10% FCS, wiping each tube with a fresh Kimwipe after pouring off the supernatant. Target cells were resuspended in DMEM-10% FBS $1x10^5$/ml.. Effector cells were adjusted to

$1x10^7$/ml in DMEM-10% FCS and 100 µl serial 3-fold dilutions of effectors were prepared in U-bottom 96-well plates. 100 µl of target cells were added per well. In order to determine spontaneous release and maximum release, six additional wells containing 100 µl of target cells were prepared for each target. Spontaneous release was revealed by incubating the target cells with 100 µl medium; maximum release was revealed by incubating the target cells with 100µl of 2% SDS. Plates were then centrifuged for 5 min at 600 rpm and incubated for 4 hours at 37^0C in 5% CO_2 and 80% humidity. After the incubation, plates were then centrifuged for 5 min at 1200 rpm. Supernatants were harvested and counted using a gamma counter. Specific lysis was determined as follows: % specific release = [(experimental release - spontaneous release)/(maximum release - spontaneous release)] x 100.

Results of the chromium release assay demonstrating specific lysis of peptide pulsed target cells are shown in figure 6.

8. Cross-reactivity with other SSX proteins:

SSX-2_{41-49} (SEQ ID NO. 15) shares a high degree of sequence identity with the same region of the other SSX proteins. The surrounding regions have also been generally well conserved. Thus the housekeeping proteasome can cleave following V_{49} in all five sequences. Moreover, SSX_{41-49} is predicted to bind HLA-A*0201 (see Table 6). CTL generated by immunization with SSX-2_{41-49} cross-react with tumor cells expressing other SSX proteins.

Table 6. SSX_{41-49} – A*0201 Predicted Binding

SEQ ID NO.	Family Member	Sequence	SYFPEITHI Score	NIH Score
15	SSX-2	KASEKIFYV	22	1017
26	SSX-1	KYSEKISYV	18	1.7
27	SSX-3	KVSEKIVYV	24	1105
28	SSX-4	KSSEKIVYV	20	82
29	SSX-5	KASEKIIYV	22	175

Example 4

Cluster Analysis ($PSMA_{163-192}$).

A peptide, AFSPQGMPEGDLVYVNYARTEDFFKLERDM, $PSMA_{163-192}$, (SEQ ID NO. 30), containing an A1 epitope cluster from prostate specific membrane antigen, $PSMA_{168-190}$ (SEQ ID NO. 31) was synthesized using standard solid-phase F-moc chemistry on a 433A ABI Peptide synthesizer. After side chain deprotection and cleavage from the resin, peptide first dissolved in formic acid and then diluted into 30% Acetic acid, was run on a reverse-phase preparative HPLC C4 column at following conditions: linear AB gradient (5% B/min) at a flow rate of 4 ml/min,

where eluent A is 0.1% aqueous TFA and eluent B is 0.1% TFA in acetonitrile. A fraction at time 16.642 min containing the expected peptide, as judged by mass spectrometry, was pooled and lyophilized. The peptide was then subjected to proteasome digestion and mass spectrum analysis essentially as described above. Prominent peaks from the mass spectra are summarized in Table 7.

Table 7. $PSMA_{163-192}$ Mass Peak Identification.

PEPTIDE	SEQUENCE	CALCULATED MASS (MH^+)
163-177	AFSPQGMPEGDLVYV	1610.0
178-189	NYARTEDFFKLE	1533.68
170-189	PEGDLVYVNYARTEDFFKLE	2406.66
178-191	NYARTEDFFKLERD	1804.95
170-191	PEGDLVYVNYARTEDFFKLERD	2677.93
178-192	NYARTEDFFKLERDM	1936.17
163-176	AFSPQGMPEGDLVY	1511.70
177-192	VNYARTEDFFKLERDM	2035.30
163-179	AFSPQGMPEGDLVYVNY	1888.12
180-192	ARTEDFFKLERDM	1658.89
163-183	AFSPQGMPEGDLVYVNYARTE	2345.61
184-192	DFFKLERDM	1201.40
176-192	YVNYARTEDFFKLERDM	2198.48
167-185	QGMPEGDLVYVNYARTEDF	2205.41
178-186	NYARTEDFF	1163.22

Boldface sequences correspond to peptides predicted to bind to MHC, see Table 8.

N-terminal Pool Sequence Analysis

One aliquot at one hour of the proteasomal digestion (see Example 3 part 3 above) was subjected to N-terminal amino acid sequence analysis by an ABI 473A Protein Sequencer (Applied Biosystems, Foster City, CA). Determination of the sites and efficiencies of cleavage was based on consideration of the sequence cycle, the repetitive yield of the protein sequencer, and the relative yields of amino acids unique in the analyzed sequence. That is if the unique (in the analyzed sequence) residue X appears only in the nth cycle a cleavage site exists n-1 residues before it in the N-terminal direction. In addition to helping resolve any ambiguity in the assignment of mass to sequences, these data also provide a more reliable indication of the relative yield of the various fragments than does mass spectrometry.

For $PSMA_{163-192}$ (SEQ ID NO. 30) this pool sequencing supports a single major cleavage site after V_{177} and several minor cleavage sites, particularly one after Y_{179}. Reviewing the results presented in figures 7A-C reveals the following:

S at the 3rd cycle indicating presence of the N-terminus of the substrate.

Q at the 5th cycle indicating presence of the N-terminus of the substrate.

N at the 1st cycle indicating cleavage after V_{177}.

N at the 3rd cycle indicating cleavage after V_{175}. Note the fragment 176-192 in Table 7.

T at the 5th cycle indicating cleavage after V_{177}.

T at the 1st –3rd cycles, indicating increasingly common cleavages after R_{181}, A_{180} and Y_{179}. Only the last of these correspond to peaks detected by mass spectrometry; 163-179 and 180-192, see Table 7. The absence of the others can indicate that they are on fragments smaller than were examined in the mass spectrum.

K at the 4th, 8th, and 10th cycles indicating cleavages after E_{183}, Y_{179}, and V_{177}, respectively, all of which correspond to fragments observed by mass spectroscopy. See Table 7.

A at the 1st and 3rd cycles indicating presence of the N-terminus of the substrate and cleavage after V_{177}, respectively.

P at the 4th and 8th cycles indicating presence of the N-terminus of the substrate.

G at the 6th and 10th cycles indicating presence of the N-terminus of the substrate.

M at the 7th cycle indicating presence of the N-terminus of the substrate and/or cleavage after F_{185}.

M at the 15th cycle indicating cleavage after V_{177}.

The 1st cycle can indicate cleavage after D_{191}, see Table 7.

R at the 4th and 13th cycle indicating cleavage after V_{177}.

R at the 2nd and 11th cycle indicating cleavage after Y_{179}.

V at the 2nd, 6th, and 13th cycle indicating cleavage after V_{175}, M_{169} and presence of the N-terminus of the substrate, respectively. Note fragments beginning at 176 and 170 in Table 7.

Y at the 1st, 2nd, and 14th cycles indicating cleavage after V_{175}, V_{177}, and presence of the N-terminus of the substrate, respectively.

L at the11th and 12th cycles indicating cleavage after V_{177}, and presence of the N-terminus of the substrate, respectively, is the interpretation most consistent with the other data. Comparing to the mass spectrometry results we see that L at the 2nd, 5th, and 9th cycles is consistent with cleavage after F_{186}, E_{183} or M_{169}, and Y_{179}, respectively. See Table 7.

Epitope Identification

Fragments co-C-terminal with 8-10 amino acid long sequences predicted to bind HLA by the SYFPEITHI or NIH algorithms were chosen for further analysis. The digestion and prediction steps of the procedure can be usefully practiced in any order. Although the substrate peptide used in proteasomal digest described here was specifically designed to include a predicted HLA-A1 binding sequence, the actual products of digestion can be checked after the fact for actual or predicted binding to other MHC molecules. Selected results are shown in Table 8.

Table 8. Predicted HLA binding by proteasomally generated fragments

SEQ ID NO	PEPTIDE	HLA	SYFPEITHI	NIH
32 & (33)	(G)MPEGDLVYV	A*0201	17 (27)	(2605)
		B*0702	20	<5
		B*5101	22	314
34 & (35)	(Q)GMPEGDLVY	A1	24 (26)	<5
		A3	16 (18)	36
		B*2705	17	25
36	MPEGDLVY	B*5101	15	NP†
37 & (38)	(P)EGDLVYVNY	A1	27 (15)	12
		A26	23 (17)	NP
39	LVYVNYARTE	A3	21	<5
40 & (41)	(Y)VNYARTEDF	A26	(20)	NP
		B*08	15	<5
		B*2705	12	50
42	NYARTEDFF	A24	NP†	100
		Cw*0401	NP	120
43	YARTEDFF	B*08	16	<5
44	RTEDFFKLE	A1	21	<5
		A26	15	NP

†No prediction

HLA-A*0201 binding assay:

HLA-A*0201 binding studies were preformed with $PSMA_{168-177}$, GMPEGDLVYV, (SEQ ID NO. 33) essentially as described in Example 3 above. As seen in figure 8, this epitope exhibits significant binding at even lower concentrations than the positive control peptides. The Melan-A peptide used as a control in this assay (and throughout this disclosure), ELAGIGILTV, is actually a variant of the natural sequence (EAAGIGILTV) and exhibits a high affinity in this assay.

Example 5

Cluster Analysis ($PSMA_{281-310}$).

Another peptide, RGIAEAVGLPSIPVHPIGYYDAQKLLEKMG, $PSMA_{281-310}$, (SEQ ID NO. 45), containing an A1 epitope cluster from prostate specific membrane antigen, $PSMA_{283-307}$ (SEQ ID NO. 46), was synthesized using standard solid-phase F-moc chemistry on a 433A ABI Peptide synthesizer. After side chain deprotection and cleavage from the resin, peptide in ddH2O

was run on a reverse-phase preparative HPLC C18 column at following conditions: linear AB gradient (5% B/min) at a flow rate of 4 ml/min, where eluent A is 0.1% aqueous TFA and eluent B is 0.1% TFA in acetonitrile. A fraction at time 17.061 min containing the expected peptide as judged by mass spectrometry, was pooled and lyophilized. The peptide was then subjected to proteasome digestion and mass spectrum analysis essentially as described above. Prominent peaks from the mass spectra are summarized in Table 9.

Table 9. $PSMA_{281-310}$ Mass Peak Identification.

PEPTIDE	SEQUENCE	CALCULATED MASS (MH^+)
281-297	RGIAEAVGLPSIPVHPI*	1727.07
286-297	AVGLPSIPVHPI**	1200.46
287-297	VGLPSIPVHPI	1129.38
288-297	GLPSIPVHPI†	1030.25
298-310	GYYDAQKLLEKMG‡	1516.5
298-305	GYYDAQKL§	958.05
281-305	RGIAEAVGLPSIPVHPIGYYDAQKL	2666.12
281-307	RGIAEAVGLPSIPVHPIGYYDAQKLLE	2908.39
286-307	AVGLPSIPVHPIGYYDAQKLLE¶	2381.78
287-307	VGLPSIPVHPIGYYDAQKLLE	2310.70
288-307	GLPSIPVHPIGYYDAQKLLE#	2211.57
281-299	RGIAEAVGLPSIPVHPIGY	1947
286-299	AVGLPSIPVHPIGY	1420.69
287-299	VGLPSIPVHPIGY	1349.61
288-299	GLPSIPVHPIGY	1250.48
287-310	VGLPSIPVHPIGYYDAQKLLEKMG	2627.14
288-310	GLPSIPVHPIGYYDAQKLLEKMG	2528.01

Boldface sequences correspond to peptides predicted to bind to MHC, see Table 10.

*By mass alone this peak could also have been 296-310 or 288-303.

**By mass alone this peak could also have been 298-307. Combination of HPLC and mass spectrometry show that at some later time points this peak is a mixture of both species.

† By mass alone this peak could also have been 289-298.

By mass alone this peak could also have been 281-295 or 294-306.

§ By mass alone this peak could also have been 297-303.

¶ By mass alone this peak could also have been 285-306.

By mass alone this peak could also have been 288-303.

None of these alternate assignments are supported N-terminal pool sequence analysis.

N-terminal Pool Sequence Analysis

One aliquot at one hour of the proteasomal digestion (see Example 3 part 3 above) was subjected to N-terminal amino acid sequence analysis by an ABI 473A Protein Sequencer (Applied Biosystems, Foster City, CA). Determination of the sites and efficiencies of cleavage was based on consideration of the sequence cycle, the repetitive yield of the protein sequencer, and the relative yields of amino acids unique in the analyzed sequence. That is if the unique (in the analyzed sequence) residue X appears only in the nth cycle a cleavage site exists n-1 residues before it in the N-terminal direction. In addition to helping resolve any ambiguity in the assignment of mass to sequences, these data also provide a more reliable indication of the relative yield of the various fragments than does mass spectrometry.

For $PSMA_{281-310}$ (SEQ ID NO. 45) this pool sequencing supports two major cleavage sites after V_{287} and I_{297} among other minor cleavage sites. Reviewing the results presented in Fig. 9 reveals the following:

S at the 4th and 11th cycles indicating cleavage after V_{287} and presence of the N-terminus of the substrate, respectively.

H at the 8th cycle indicating cleavage after V_{287}. The lack of decay in peak height at positions 9 and 10 versus the drop in height present going from 10 to 11 can suggest cleavage after A_{286} and E_{285} as well, rather than the peaks representing latency in the sequencing reaction.

D at the 2nd, 4th, and 7th cycles indicating cleavages after Y_{299}, I_{297}, and V_{294}, respectively. This last cleavage is not observed in any of the fragments in Table 10 or in the alternate assignments in the notes below.

Q at the 6th cycle indicating cleavage after I_{297}.

M at the 10th and 12th cycle indicating cleavages after Y_{299} and I_{297}, respectively.

Epitope Identification

Fragments co-C-terminal with 8-10 amino acid long sequences predicted to bind HLA by the SYFPEITHI or NIH algorithms were chosen for further study. The digestion and prediction steps of the procedure can be usefully practiced in any order. Although the substrate peptide used in proteasomal digest described here was specifically designed to include a predicted HLA-A1 binding sequence, the actual products of digestion can be checked after the fact for actual or predicted binding to other MHC molecules. Selected results are shown in Table 10.

Table 10.
Predicted HLA binding by proteasomally generated fragments: $PSMA_{281-310}$

SEQ ID NO.	PEPTIDE	HLA	SYFPEITHI	NIH
47 & (48)	(G)LPSIPVH	A*0201	16 (24)	(24)

was run on a reverse-phase preparative HPLC C18 column at following conditions: linear AB gradient (5% B/min) at a flow rate of 4 ml/min, where eluent A is 0.1% aqueous TFA and eluent B is 0.1% TFA in acetonitrile. A fraction at time 17.061 min containing the expected peptide as judged by mass spectrometry, was pooled and lyophilized. The peptide was then subjected to proteasome digestion and mass spectrum analysis essentially as described above. Prominent peaks from the mass spectra are summarized in Table 9.

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PEPTIDE	SEQUENCE	CALCULATED MASS (MH^+)
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286-297	AVGLPSIPVHPI**	1200.46
287-297	VGLPSIPVHPI	1129.38
288-297	GLPSIPVHPI†	1030.25
298-310	GYYDAQKLLEKMG‡	1516.5
298-305	GYYDAQKL§	958.05
281-305	RGIAEAVGLPSIPVHPIGYYDAQKL	2666.12
281-307	RGIAEAVGLPSIPVHPIGYYDAQKLLE	2908.39
286-307	AVGLPSIPVHPIGYYDAQKLLE¶	2381.78
287-307	VGLPSIPVHPIGYYDAQKLLE	2310.70
288-307	GLPSIPVHPIGYYDAQKLLE#	2211.57
281-299	RGIAEAVGLPSIPVHPIGY	1947
286-299	AVGLPSIPVHPIGY	1420.69
287-299	VGLPSIPVHPIGY	1349.61
288-299	GLPSIPVHPIGY	1250.48
287-310	VGLPSIPVHPIGYYDAQKLLEKMG	2627.14
288-310	GLPSIPVHPIGYYDAQKLLEKMG	2528.01

Boldface sequences correspond to peptides predicted to bind to MHC, see Table 10.

*By mass alone this peak could also have been 296-310 or 288-303.

**By mass alone this peak could also have been 298-307. Combination of HPLC and mass spectrometry show that at some later time points this peak is a mixture of both species.

† By mass alone this peak could also have been 289-298.
By mass alone this peak could also have been 281-295 or 294-306.

§ By mass alone this peak could also have been 297-303.

¶ By mass alone this peak could also have been 285-306.

By mass alone this peak could also have been 288-303.

None of these alternate assignments are supported N-terminal pool sequence analysis.

N-terminal Pool Sequence Analysis

One aliquot at one hour of the proteasomal digestion (see Example 3 part 3 above) was subjected to N-terminal amino acid sequence analysis by an ABI 473A Protein Sequencer (Applied Biosystems, Foster City, CA). Determination of the sites and efficiencies of cleavage was based on consideration of the sequence cycle, the repetitive yield of the protein sequencer, and the relative yields of amino acids unique in the analyzed sequence. That is if the unique (in the analyzed sequence) residue X appears only in the nth cycle a cleavage site exists n-1 residues before it in the N-terminal direction. In addition to helping resolve any ambiguity in the assignment of mass to sequences, these data also provide a more reliable indication of the relative yield of the various fragments than does mass spectrometry.

For $PSMA_{281-310}$ (SEQ ID NO. 45) this pool sequencing supports two major cleavage sites after V_{287} and I_{297} among other minor cleavage sites. Reviewing the results presented in Fig. 9 reveals the following:

S at the 4th and 11th cycles indicating cleavage after V_{287} and presence of the N-terminus of the substrate, respectively.

H at the 8th cycle indicating cleavage after V_{287}. The lack of decay in peak height at positions 9 and 10 versus the drop in height present going from 10 to 11 can suggest cleavage after A_{286} and E_{285} as well, rather than the peaks representing latency in the sequencing reaction.

D at the 2nd, 4th, and 7th cycles indicating cleavages after Y_{299}, I_{297}, and V_{294}, respectively. This last cleavage is not observed in any of the fragments in Table 10 or in the alternate assignments in the notes below.

Q at the 6th cycle indicating cleavage after I_{297}.

M at the 10th and 12th cycle indicating cleavages after Y_{299} and I_{297}, respectively.

Epitope Identification

Fragments co-C-terminal with 8-10 amino acid long sequences predicted to bind HLA by the SYFPEITHI or NIH algorithms were chosen for further study. The digestion and prediction steps of the procedure can be usefully practiced in any order. Although the substrate peptide used in proteasomal digest described here was specifically designed to include a predicted HLA-A1 binding sequence, the actual products of digestion can be checked after the fact for actual or predicted binding to other MHC molecules. Selected results are shown in Table 10.

Table 10.
Predicted HLA binding by proteasomally generated fragments: $PSMA_{281-310}$

SEQ ID NO.	PEPTIDE	HLA	SYFPEITHI	NIH
47 & (48)	(G) LPSIPVH	A*0201	16 (24)	(24)

	PI			
		B*0702/B7	23	12
		B*5101	24	572
		Cw*0401	NP†	20
49 & (50)	(P) IGYYDAQ KL	A*0201	(16)	<5
		A26	(20)	NP
		B*2705	16	25
		B*2709	15	NP
		B*5101	21	57
		Cw*0301	NP	24
51 & (52)	(P) SIPVHPI GY	A1	21 (27)	<5
		A26	22	NP
		A3	16	<5
53	IPVHPIGY	B*5101	16	NP
54	YYDAQKLLE	A1	22	<5

†No prediction

As seen in Table 10, N-terminal addition of authentic sequence to epitopes can often generate still useful, even better epitopes, for the same or different MHC restriction elements. Note for example the pairing of (G)LPSIPVHPI with HLA-A*0201, where the 10-mer can be used as a vaccine useful with several MHC types by relying on N-terminal trimming to create the epitopes for HLA-B7, -B*5101, and Cw*0401.

HLA-A*0201 binding assay:

HLA-A*0201 binding studies were preformed with $PSMA_{288-297}$, GLPSIPVHPI, (SEQ ID NO. 48) essentially as described in Examples 3 and 4 above. As seen in figure 8, this epitope exhibits significant binding at even lower concentrations than the positive control peptides.

Example 6

Cluster Analysis ($PSMA_{454-481}$).

Another peptide, SSIEGNYTLRVDCTPLMYSLVHLTKEL, $PSMA_{454-481}$, (SEQ ID NO. 55) containing an epitope cluster from prostate specific membrane antigen, was synthesized by MPS (purity >95%) and subjected to proteasome digestion and mass spectrum analysis as described above. Prominent peaks from the mass spectra are summarized in Table 11.

Table 11. $PSMA_{454-481}$ Mass Peak Identification.

MS PEAK (measured)	PEPTIDE	SEQUENCE	CALCULATED MASS (MH^+)
1238.5	454-464	SSIEGNYTLRV	1239.78
1768.38±0.60	454-469	SSIEGNYTLRVDCTPL	1768.99
1899.8	454-470	SSIEGNYTLRVDCTPLM	1900.19
1097.63±0.91	463-471	RVDCTPLMY	1098.32
2062.87±0.68	454-471*	SSIEGNYTLRVDCTPLMY	2063.36
1153	472-481**	SLVHNLTKEL	1154.36
1449.93±1.79	470-481	MYSLVHNLTKEL	1448.73

Boldface sequence correspond to peptides predicted to bind to MHC, see Table 12.
* On the basis of mass alone this peak could equally well be assigned to the peptide 455-472 however proteasomal removal of just the N-terminal amino acid is considered unlikely. If the issue were important it could be resolved by N-terminal sequencing.
**On the basis of mass this fragment might also represent 455-464.

Epitope Identification

Fragments co-C-terminal with 8-10 amino acid long sequences predicted to bind HLA by the SYFPEITHI or NIH algorithms were chosen for further study. The digestion and prediction steps of the procedure can be usefully practiced in any order. Although the substrate peptide used in proteasomal digest described here was specifically designed to include predicted HLA-A2.1 binding sequences, the actual products of digestion can be checked after the fact for actual or predicted binding to other MHC molecules. Selected results are shown in Table 12.

Table 12. Predicted HLA binding by proteasomally generated fragments

SEQ ID NO	PEPTIDE	HLA	SYFPEITHI	NIH
56 & (57)	(S) IEGNYTLRV	A1	(19)	<5
58	EGNYTLRV	A*0201	16 (22)	<5
		B*5101	15	NP†
59 & (60)	(Y) TLRVDCTPL	A*0201	20 (18)	(5)
		A26	16 (18)	NP
		B7	14	40
		B8	23	<5
		B*2705	12	30
		Cw*0301	NP	(30)
61	LRVDCTPLM	B*2705	20	600
		B*2709	20	NP
62 & (63)	(L) RVDCTPLMY	A1	32 (22)	125 (13.5)
		A3	25	<5

		A26	22	NP
		B*2702	NP	(200)
		B*2705	13 (NP)	(1000)

†No prediction

As seen in Table 12, N-terminal addition of authentic sequence to epitopes can often generate still useful, even better epitopes, for the same or different MHC restriction elements. Note for example the pairing of (L)RVDCTPLMY (SEQ ID NOS 62 and (63)) with HLA-B*2702/5, where the 10-mer has substantial predicted halftimes of dissociation and the co-C-terminal 9-mer does not. Also note the case of SIEGNYTLRV (SEQ ID NO 57) a predicted HLA-A*0201 epitope which can be used as a vaccine useful with HLA-B*5101 by relying on N-terminal trimming to create the epitope.

HLA-A*0201 binding assay

HLA-A*0201 binding studies were preformed, essentially as described in Example 3 above, with $PSMA_{460-469}$, TLRVDCTPL, (SEQ ID NO. 60). As seen in figure 10, this epitope was found to bind HLA-A2.1 to a similar extent as the known A2.1 binder FLPSDYFPSV (HBV_{18-27}; SEQ ID NO: 24) used as a positive control. Additionally, $PSMA_{461-469}$, (SEQ ID NO. 59) binds nearly as well.

ELISPOT analysis: $\underline{PSMA_{463-471}}$ (SEQ ID NO. 62)

The wells of a nitrocellulose-backed microtiter plate were coated with capture antibody by incubating overnight at 4°C using 50 µl/well of 4µg/ml murine anti-human γ-IFN monoclonal antibody in coating buffer (35 mM sodium bicarbonate, 15 mM sodium carbonate, pH 9.5). Unbound antibody was removed by washing 4 times 5 min. with PBS. Unbound sites on the membrane then were blocked by adding 200µl/well of RPMI medium with 10% serum and incubating 1 hr. at room temperature. Antigen stimulated $CD8^+$ T cells, in 1:3 serial dilutions, were seeded into the wells of the microtiter plate using 100µl/well, starting at $2x10^5$ cells/well. (Prior antigen stimulation was essentially as described in Scheibenbogen, C. et al. *Int. J. Cancer* 71:932-936, 1997. $PSMA_{462-471}$ (SEQ ID NO. 62) was added to a final concentration of 10µg/ml and IL-2 to 100 U/ml and the cells cultured at 37°C in a 5% CO_2, water-saturated atmosphere for 40 hrs. Following this incubation the plates were washed with 6 times 200 µl/well of PBS containing 0.05% Tween-20 (PBS-Tween). Detection antibody, 50µl/well of 2g/ml biotinylated murine anti-human γ-IFN monoclonal antibody in PBS+10% fetal calf serum, was added and the plate incubated at room temperature for 2 hrs. Unbound detection antibody was removed by washing with 4 times 200 µl of PBS-Tween. 100µl of avidin-conjugated horseradish peroxidase (Pharmingen, San Diego, CA) was added to each well and incubated at room temperature for 1 hr.

Unbound enzyme was removed by washing with 6 times 200 µl of PBS-Tween. Substrate was prepared by dissolving a 20 mg tablet of 3-amino 9-ethylcoarbasole in 2.5 ml of N, N-dimethylformamide and adding that solution to 47,5 ml of 0.05 M phosphate-citrate buffer (pH 5.0). 25 µl of 30% H_2O_2 was added to the substrate solution immediately before distributing substrate at100 µl/well and incubating the plate at room temperature. After color development (generally 15-30 min.), the reaction was stopped by washing the plate with water. The plate was air dried and the spots counted using a stereomicroscope.

Figure 11 shows the detection of $PSMA_{463-471}$ (SEQ ID NO. 62)-reactive HLA-A1$^+$ CD8$^+$ T cells previously generated in cultures of HLA-A1$^+$ CD8$^+$ T cells with autologous dendritic cells plus the peptide. No reactivity is detected from cultures without peptide (data not shown). In this case it can be seen that the peptide reactive T cells are present in the culture at a frequency between 1 in $2.2x10^4$ and 1 in $6.7x10^4$. That this is truly an HLA-A1-restricted response is demonstrated by the ability of anti-HLA-A1 monoclonal antibody to block γ-IFN production; see figure 12.

Example 7

Cluster Analysis ($PSMA_{653-687}$).

Another peptide, FDKSNPIVLRMMNDQLMFLERAFIDPLGLPDRPFY $PSMA_{653-687}$, (SEQ ID NO. 64) containing an A2 epitope cluster from prostate specific membrane antigen, $PSMA_{660-681}$ (SEQ ID NO 65), was synthesized by MPS (purity >95%) and subjected to proteasome digestion and mass spectrum analysis as described above. Prominent peaks from the mass spectra are summarized in Table 13.

Table 13. $PSMA_{653-687}$ Mass Peak Identification.

MS PEAK (measured)	PEPTIDE	SEQUENCE	CALCULATED MASS (MH^+)
906.17±0.65	681-687**	LPDRPFY	908.05
1287.73±0.76	677-687**	DPLGLPDRPFY	1290.47
1400.3±1.79	676-687	IDPLGLPDRPFY	1403.63
1548.0±1.37	675-687	FIDPLGLPDRPFY	1550.80
1619.5±1.51	674-687**	AFIDPLGLPDRPFY	1621.88
1775.48±1.32	673-687*	RAFIDPLGLPDRPFY	1778.07
2440.2±1.3	653-672	FDKSNPIVLRMMNDQLMFLE	2442.93

1904.63±1.56	672-687*	ERAFIDPLGLPDRPFY	1907.19
2310.6±2.5	653-671	FDKSNPIVLRMMNDQLMFL	2313.82
2017.4±1.94	671-687	LERAFIDPLGLPDRPFY	2020.35
2197.43±1.78	653-670	FDKSNPIVLRMMNDQLMF	2200.66

Boldface sequence correspond to peptides predicted to bind to MHC, see Table 13.
* On the basis of mass alone this peak could equally well be assigned to a peptide beginning at 654, however proteasomal removal of just the N-terminal amino acid is considered unlikely. If the issue were important it could be resolved by N-terminal sequencing.
** On the basis of mass alone these peaks could have been assigned to internal fragments, but given the overall pattern of digestion it was considered unlikely.

Epitope Identification

Fragments co-C-terminal with 8-10 amino acid long sequences predicted to bind HLA by the SYFPEITHI or NIH algorithms were chosen for further study. The digestion and prediction steps of the procedure can be usefully practiced in any order. Although the substrate peptide used in proteasomal digest described here was specifically designed to include predicted HLA-A2.1 binding sequences, the actual products of digestion can be checked after the fact for actual or predicted binding to other MHC molecules. Selected results are shown in Table 14.

Table 14. Predicted HLA binding by proteasomally generated fragments

SEQ ID NO	PEPTIDE	HLA	SYFPEITHI	NIH
66 & (67)	(R)MMNDQLMFL	A*0201	24 (23)	1360 (722)
		A*0205	NP†	71 (42)
		A26	15	NP
		B*2705	12	50
68	RMMNDQLMF	B*2705	17	75

†No prediction

As seen in Table 14, N-terminal addition of authentic sequence to epitopes can generate still useful, even better epitopes, for the same or different MHC restriction elements. Note for example the pairing of (R)MMNDQLMFL (SEQ ID NOS. 66 and (67)) with HLA-A*02, where the 10-mer retains substantial predicted binding potential.

HLA-A*0201 binding assay

HLA-A*0201 binding studies were preformed, essentially as described in Example 3 above, with $PSMA_{663-671}$, (SEQ ID NO. 66) and $PSMA_{662-671}$, RMMNDQLMFL (SEQ NO. 67). As

seen in figures 10, 13 and 14, this epitope exhibits significant binding at even lower concentrations than the positive control peptide (FLPSDYFPSV (HBV_{18-27}); SEQ ID NO: 24). Though not run in parallel, comparison to the controls suggests that $PSMA_{662-671}$ (which approaches the Melan A peptide in affinity) has the superior binding activity of these two PSMA peptides.

Example 8

Vaccinating with epitope vaccines.

1. Vaccination with peptide vaccines:

A. Intranodal delivery

A formulation containing peptide in aqueous buffer with an antimicrobial agent, an antioxidant, and an immunomodulating cytokine, was injected continuously over several days into the inguinal lymph node using a miniature pumping system developed for insulin delivery (MiniMed; Northridge, CA). This infusion cycle was selected in order to mimic the kinetics of antigen presentation during a natural infection.

B. Controlled release

A peptide formulation is delivered using controlled PLGA microspheres as is known in the art, which alter the pharmacokinetics of the peptide and improve immunogenicity. This formulation is injected or taken orally.

C. Gene gun delivery

A peptide formulation is prepared wherein the peptide is adhered to gold microparticles as is known in the art. The particles are delivered in a gene gun, being accelerated at high speed so as to penetrate the skin, carrying the particles into dermal tissues that contain pAPCs.

D. Aerosol delivery

A peptide formulation is inhaled as an aerosol as is known in the art, for uptake into appropriate vascular or lymphatic tissue in the lungs.

2. Vaccination with nucleic acid vaccines:

A nucleic acid vaccine is injected into a lymph node using a miniature pumping system, such as the MiniMed insulin pump. A nucleic acid construct formulated in an aqueous buffered solution containing an antimicrobial agent, an antioxidant, and an immunomodulating cytokine, is delivered over a several day infusion cycle in order to mimic the kinetics of antigen presentation during a natural infection.

Optionally, the nucleic acid construct is delivered using controlled release substances, such as PLGA microspheres or other biodegradable substances. These substances are injected or taken orally. Nucleic acid vaccines are given using oral delivery, priming the immune response through uptake into GALT tissues. Alternatively, the nucleic acid vaccines are delivered using a gene gun,

wherein the nucleic acid vaccine is adhered to minute gold particles. Nucleic acid constructs can also be inhaled as an aerosol, for uptake into appropriate vascular or lymphatic tissue in the lungs.

Example 9

Assays for the effectiveness of epitope vaccines.

1. Tetramer analysis:

Class I tetramer analysis is used to determine T cell frequency in an animal before and after administration of a housekeeping epitope. Clonal expansion of T cells in response to an epitope indicates that the epitope is presented to T cells by pAPCs. The specific T cell frequency is measured against the housekeeping epitope before and after administration of the epitope to an animal, to determine if the epitope is present on pAPCs. An increase in frequency of T cells specific to the epitope after administration indicates that the epitope was presented on pAPC.

2. Proliferation assay:

Approximately 24 hours after vaccination of an animal with housekeeping epitope, pAPCs are harvested from PBMCs, splenocytes, or lymph node cells, using monoclonal antibodies against specific markers present on pAPCs, fixed to magnetic beads for affinity purification. Crude blood or splenoctye preparation is enriched for pAPCs using this technique. The enriched pAPCs are then used in a proliferation assay against a T cell clone that has been generated and is specific for the housekeeping epitope of interest. The pAPCs are coincubated with the T cell clone and the T cells are monitored for proliferation activity by measuring the incorporation of radiolabeled thymidine by T cells. Proliferation indicates that T cells specific for the housekeeping epitope are being stimulated by that epitope on the pAPCs.

3. Chromium release assay:

A human patient, or non-human animal genetically engineered to express human class I MHC, is immunized using a housekeeping epitope. T cells from the immunized subject are used in a standard chromium release assay using human tumor targets or targets engineered to express the same class I MHC. T cell killing of the targets indicates that stimulation of T cells in a patient would be effective at killing a tumor expressing a similar TuAA.

Example 10

Induction of CTL response with naked DNA is efficient by Intra-lymph node immunization.

In order to quantitatively compare the $CD8^+$ CTL responses induced by different routes of immunization a plasmid DNA vaccine (pEGFPL33A) containing a well-characterized immunodominant CTL epitope from the LCMV-glycoprotein (G) (gp33; amino acids 33-41) (Oehen, S., et al.. *Immunology* 99, 163-169 2000) was used, as this system allows a comprehensive assessment of antiviral CTL responses. Groups of 2 C57BL/6 mice were immunized once with

titrated doses (200-0.02μg) of pEGFPL33A DNA or of control plasmid pEGFP-N3, administered i.m. (intramuscular), i.d. (intradermal), i.spl. (intrasplenic), or i.ln. (intra-lymph node). Positive control mice received 500 pfu LCMV i.v. (intravenous). Ten days after immunization spleen cells were isolated and gp33-specific CTL activity was determined after secondary *in vitro* restimulation. As shown in Fig. 15, i.m. or i.d. immunization induced weakly detectable CTL responses when high doses of pEFGPL33A DNA (200μg) were administered. In contrast, potent gp33-specific CTL responses were elicited by immunization with only 2μg pEFGPL33A DNA i.spl. and with as little as 0.2μg pEFGPL33A DNA given i.ln. (figure 15; symbols represent individual mice and one of three similar experiments is shown). Immunization with the control pEGFP-N3 DNA did not elicit any detectable gp33-specific CTL responses (data not shown).

Example 11

Intra-lymph node DNA immunization elicits anti-tumor immunity.

To examine whether the potent CTL responses elicited following i.ln. immunization were able to confer protection against peripheral tumors, groups of 6 C57BL/6mice were immunized three times at 6-day intervals with 10μg of pEFGPL33A DNA or control pEGFP-N3 DNA. Five days after the last immunization small pieces of solid tumors expressing the gp33 epitope (EL4-33) were transplanted s.c. into both flanks and tumor growth was measured every 3-4d. Although the EL4-33 tumors grew well in mice that had been repetitively immunized with control pEGFP-N3 DNA (figure 16), mice which were immunized with pEFGPL33A DNA i.ln. rapidly eradicated the peripheral EL4-33 tumors (figure 16).

Example 12

Differences in lymph node DNA content mirrors differences in CTL response following intra-lymph node and intramuscular injection.

pEFGPL33A DNA was injected i.ln. or i.m. and plasmid content of the injected or draining lymph node was assessed by real time PCR after 6, 12, 24, 48 hours, and 4 and 30 days. At 6, 12, and 24 hours the plasmid DNA content of the injected lymph nodes was approximately three orders of magnitude greater than that of the draining lymph nodes following i.m. injection. No plasmid DNA was detectable in the draining lymph node at subsequent time points (Fig. 17). This is consonant with the three orders of magnitude greater dose needed using i.m. as compared to i.ln. injections to achieve a similar levels of CTL activity. $CD8^{-/-}$ knockout mice, which do not develop a CTL response to this epitope, were also injected i.ln. showing clearance of DNA from the lymph node is not due to $CD8^{+}$ CTL killing of cells in the lymph node. This observation also supports the conclusion that i.ln. administration will not provoke immunopathological damage to the lymph node.

Example 13

Administration of a DNA plasmid formulation of a therapeutic vaccine for melanoma to humans.

SYNCHROTOPE TA2M, a melanoma vaccine, encoding the HLA-A2-restricted tyrosinase epitope SEQ ID NO. 1 and epitope cluster SEQ ID NO. 69, was formulated in 1% Benzyl alcohol, 1% ethyl alcohol, 0.5mM EDTA, citrate-phosphate, pH 7.6. Aliquots of 80, 160, and 320 μg DNA/ml were prepared for loading into MINIMED 407C infusion pumps. The catheter of a SILHOUETTE infusion set was placed into an inguinal lymph node visualized by ultrasound imaging. The assembly of pump and infusion set was originally designed for the delivery of insulin to diabetics and the usual 17mm catheter was substituted with a 31mm catheter for this application. The infusion set was kept patent for 4 days (approximately 96 hours) with an infusion rate of about 25 μl/hour resulting in a total infused volume of approximately 2.4 ml. Thus the total administered dose per infusion was approximately 200, and 400 μg; and can be 800 μg, respectively, for the three concentrations described above. Following an infusion subjects were given a 10 day rest period before starting a subsequent infusion. Given the continued residency of plasmid DNA in the lymph node after administration (as in example 12) and the usual kinetics of CTL response following disappearance of antigen, this schedule will be sufficient to maintain the immunologic CTL response.

Example 14

Additional Epitopes.

The methodologies described above, and in particular in examples 3-7, have been applied to additional synthetic peptide substrates, leading to the identification of further epitopes as set for the in tables 15-36 below. The substrates used here were designed to identify products of housekeeping proteasomal processing that give rise to HLA-A*0201 binding epitopes, but additional MHC-binding reactivities can be predicted, as discussed above. Many such reactivities are disclosed, however, these listings are meant to be exemplary, not exhaustive or limiting. As also discussed above, individual components of the analyses can be used in varying combinations and orders. The digests of the NY-ESO-1 substrates 136-163 and 150-177 (SEQ ID NOS. 254 and 255, respectively) yielded fragments that did not fly well in MALDI-TOF mass spectrometry. However, they were quite amenable to N-terminal peptide pool sequencing, thereby allowing identification of cleavage sites. Not all of the substrates necessarily meet the formal definition of an epitope cluster as referenced in example 3. Some clusters are so large, e.g. NY-ESO-$1_{86\text{-}171}$, that it was more convenient to use substrates spanning only a portion of this cluster. In other cases, substrates were extended beyond clusters meeting the formal definition to include neighboring

predicted epitopes. In some instances, actual binding activity may have dictated what substrate was made, as with for example the MAGE epitopes reported here, where HLA binding activity was determined for a selection of peptides with predicted affinity, before synthetic substrates were designed.

Table 15

GP100: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

†Scores are given from the two binding prediction programs referenced above (see example 3).

			SEQ ID	HLA Binding Predictions (SYFPEITHI /NIH)†					
Substrate	**Epitope**	**Sequence**	**NO**	**A*0201**	**A1**	**A3**	**B7**	**B8**	**Comments**
609-644	630-638*	LPHSSSHWL	88				20/80	16/<5	*The digestion of 609-644 and 622-650 have generated the same epitopes.
	629-638*	QLPHSSSHWL	89	21/117					
	614-622	LIYRRRLMK	90			32/20			
	613-622	SLIYRRRLMK	91	14/<5		29/60			
	615-622	IYRRRLMK	92					15/<5	
622-650	630-638*	LPHSSSHWL	93				20/80	16/<5	
	629-638*	QLPHSSSHWL	94	21/117					

Table 16A

MAGE-1: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

			SEQ ID NO	HLA Binding Predictions (SYFPEITHI /NIH)†					
Substrate	Epitope	Sequence		A*0201	A1	A3	B7	B8	Other
86-109	95-102	ESLFRAVI	95					16/<5	
	93-102	ILESLFRAVI	96	21/<5		20/<5			
	93-101	ILESLFRAV	97	23/<5					
	92-101	CILESLFRAV	98	23/55					
	92-100	CILESLFRA	99	20/138					
263-292	263-271	EFLWGPRAL	100						A26 (R 21), A24 (NIH 30)
	264-271	FLWGPRAL	101					17/<5	
	264-273	FLWGPRALAE	102	16/<5		19/<5			
	265-274	LWGPRALAET	103	16/<5					
	268-276	PRALAETSY	104	15/<5					
	267-276	GPRALAETSY	105	15/<5			<15/<5		B4403 (NIH 7); B3501 (NIH 120)
	269-277	RALAETSYV	106	18/20					
	271-279	LAETSYVKV	107	19/<5					
	270-279	ALAETSYVKV	108	30/427		19/<5<5			
	272-280	AETSYVKVL	109	15/<5					B4403 (NIH 36)
	271-280	LAETSYVKVL	110	18/<5			<15/<5		
	274-282	TSYVKVLEY	111		26/<5				B4403 (NIH 14)
	273-282	ETSYVKVLEY	112		28/6				A26 (R 31), B4403 (NIH 14)
	278-286	KVLEYVIKV	113	26/743		16/<5			

Table 16B
MAGE-1: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	SEQ ID NO	HLA Binding Predictions (SYFPEITHI /NIH)†					
				A*0201	A1	A3	B7	B8	Other
168-193	168-177	SYVLVTCLGL	114						A24 (NIH 300)
	169-177	YVLVTCLGL	115	20/32		15/<5	<15/20		
	170-177	VLVTCLGL	116					17/<5	
229-258	240-248	TQDLVQEKY	117		29/<5				
	239-248	LTQDLVQEKY	118		23/<5				A26 (R 22)
	232-240	YGEPRKLLT	119		24/11				
	243-251	LVQEKYLEY	120		21/<5	21/<5			A26 (R 28)
	242-251	DLVQEKYLEY	121		22/<5	19/<5			A26 (R 30)
	230-238	SAYGEPRKL	122	21/<5					B5101 (25/121)
272-297	278-286	KVLEYVIKV	123	26/743		16/<5			
	277-286	VKVLEYVIKV	124	17/<5					
	276-284	YVKVLEYVI	125	15/<5		15/<5		17/<5	
	274-282	TSYVKVLEY	126		26/<5				
	273-282	ETSYVKVLEY	127		28/6				
	283-291	VIKVSARVR	128			20/<5			
	282-291	YVIKVSARVR	129			24/<5			

†Scores are given from the two binding prediction programs referenced above (see example 3). R indicates a SYFPEITHI score.

Table 17A

MAGE-2: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	SEQ ID NO	HLA Binding Predictions (SYFPEITHI /NIH)†					
				A*0201	A1	A3	B7	B8	Other
107-126	115-122	ELVHFLLL	130					18/<5	
	113-122	MVELVHFLLL	131		21/<5				A26 (R 22)
	109-116	ISRKMVEL	132					17/<5	
	108-116	AISRKMVEL	133	25/7		19/<5	16/12	26/<5	
	107-116	AAISRKMVEL	134	22/<5			14/36	n.p./16	
	112-120	KMVELVHFL	135	27/2800					
	109-117	ISRKMVELV	136	16/<5					
	108-117	AISRKMVELV	137	24/11					
	116-124	LVHFLLLKY	138		23/<5	19/<5			A26 (R 26)
	115-124	ELVHFLLLKY	139		24/<5	19/5			A26 (R 29)
	111-119	RKMVELVHF	140						
145-175	158-166	LQLVFGIEV	141	17/168					
	157-166	YLQLVFGIEV	142	24/1215					
	159-167	QLVFGIEVV	143	25/32		18/<5			
	158-167	LQLVFGIEVV	144	18/20					
	164-172	IEVVEVVPI	145	16/<5					
	163-172	GIEVVEVVPI	146	22/<5					
	162-170	FGIEVVEVV	147	19/<5					B5101(24/69.212)
	154-162	ASEYLQLVF	148		22/68				
	153-162	KASEYLQLVF	149			15/<5			

†Scores are given from the two binding prediction programs referenced above (see example 3). R indicates a SYFPEITHI score.

Table 17B
MAGE-2: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

				HLA Binding Predictions (SYFPEITHI /NIH)†					
Substrate	**Epitope**	**Sequence**		**A*0201**	**A1**	**A3**	**B7**	**B8**	**Other**
213-233	218-225	EEKIWEEL	150					**22/<5**	
	216-225	APEEKIWEEL	151	**15/<5**			**22/72**		
	216-223	APEEKIWE	152					**18/<5**	
	220-228	KIWEELSML	153	**26/804**		**16/<5**		**16/<5**	A26 (R 26)
	219-228	EKIWEELSML	154						A26 (R 22)
271-291	271-278	FLWGPRAL	155					**17/<5**	
	271-279	FLWGPRALI	156	**25/398**		**16/7**			
	278-286	LIETSYVKV	157	**23/<5**					
	277-286	ALIETSYVKV	158	**30/427**		**21/<5**			
	276-284	RALIETSYV	159	**18/19**					B5101 (20/55)
	279-287	IETSYVKVL	160	**15/<5**					
	278-287	LIETSYVKVL	161	**22/<5**					A26 (R 22)

†Scores are given from the two binding prediction programs referenced above (see example 3). R indicates a SYFPEITHI score.

Table 18

MAGE-3: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	SEQ ID NO	HLA Binding Predictions (SYFPEITHI /NIH)†					
				A*0201	A1	A3	B7	B8	Other
267-286	271-278	FLWGPRAL	162					17/<5	
	270-278	EFLWGPRAL	163						A26 (R 21); A24 (NIH 30)
	271-279	FLWGPRALV	164	27/2655		16/<5			
	276-284	RALVETSYV	165	18/19					B5101 (20/55)
	272-280	LWGPRALVE	166			15/<5			
	271-280	FLWGPRALVE	167	15/<5		22/<5			
	272-281	LWGPRALVET	168	16/<5					

†Scores are given from the two binding prediction programs referenced above (see example 3). R indicates a SYFPEITHI score.

Table 19A
NY-ESO-1: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	SEQ ID NO	HLA Binding Predictions (SYFPEITHI /NIH)†					
				A*0201	A1	A3	B7	B8	Other
81-113	82-90	GPESRLLEF	169		16/11		18/<5	22/<5	
	83-91	PESRLLEFY	170		15/<5				B4403 (NIH 18)
	82-91	GPESRLLEFY	171		25/11				
	84-92	ESRLLEFYL	172					19/8	
	86-94	RLLEFYLAM	173	21/430		21/<5			
	88-96	LEFYLAMPF	174						B4403 (NIH 60)
	87-96	LLEFYLAMPF	175		<15/45	18/<5			
	93-102	AMPFATPMEA	176	15/<5					
	94-102	MPFATPMEA	177				17/<5		
101-133	115-123	PLPVPGVLL	178	20/<5		17/<5	16/<5	18/<5	
	114-123	PPLPVPGVLL	179				23/12		
	116-123*	LPVPGVLL	180					16/<5	Comment *Evidence of the same epitope obtained from two digests.
	103-112	ELARRSLAQD	181	15/<5		20/<5			
	118-126*	VPGVLLKEF	182				17/<5	16/<5	
	117-126*	PVPGVLLKEF	183			16/<5			
116-145	116-123*	LPVPGVLL	184					16/<5	
	127-135	TVSGNILTI	185	21/<5		19/<5			
	126-135	FTVSGNILTI	186	20/<5					
	120-128	GVLLKEFTV	187	20/130		18/<5			
	121-130	VLLKEFTVSG	188	17/<5		18/<5			
	122-130	LLKEFTVSG	189	20/<5		18/<5			
	118-126*	VPGVLLKEF	190				17/<5	16/<5	
	117-126*	PVPGVLLKEF	191			16/<5			

†Scores are given from the two binding prediction programs referenced above (see example 3).

Table 19B
NY-ESO-1: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	SEQ ID NO	HLA Binding Predictions (SYFPEITHI /NIH)†					
				A*0201	A1	A3	B7	B8	Other
136-163 (SEQ ID NO 254)	139-147	AADHRQLQL	192	17/<5	17/<5			22/<5	
	148-156	SISSCLQQL	193	24/7					A26 (R 25)
	147-156	LSISSCLQQL	194	18/<5					
	138-147	TAADHRQLQL	195	18/<5					
150-177 (SEQ ID NO 255)	161-169	WITQCFLPV	196	18/84					
	157-165	SLLMWITQC	197	18/42		17/<5			
	150-158	SSCLQQLSL	198	15/<5					
	154-162	QQLSLLMWI	199	15/50					
	151-159	SCLQQLSLL	200	18/<5					
	150-159	SSCLQQLSLL	201	16/<5					
	163-171	TQCFLPVFL	202	<15/12					
	162-171	ITQCFLPVFL	203	18/<5					A26 (R 19)

†Scores are given from the two binding prediction programs referenced above (see example 3). R indicates a SYFPEITHI score

Table 20
PRAME: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	SEQ ID NO	HLA Binding Predictions (SYFPEITHI /NIH)†					
				A*0201	A1	A3	B7	B8	Other
211-245	219-227	PMQDIKMIL	204	16/<5				16/n.d.	A26 (R 20)
	218-227	MPMQDIKMIL	205				<15/240		
411-446	428-436	QHLIGLSNL	206	18/<5					
	427-436	LQHLIGLSNL	207	16/8					
	429-436	HLIGLSNL	208					17/<5	B15 (R 21)
	431-439	IGLSNLTHV	209	18/7					B*5101 (R 22)
	430-439	LIGLSNLTHV	210	24/37					

†Scores are given from the two binding prediction programs referenced above (see example 3). R indicates a SYFPEITHI score.

Table 21
PSA: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	SEQ ID NO	HLA Binding Predictions (SYFPEITHI /NIH)†					
				A*0201	A1	A3	B7	B8	Other
42-77	53-61	VLVHPQWVL	211	22/112			<15/6	17/<5	
	52-61	GVLVHPQWVL	212	17/21		16/<5	<15/30		A26 (R 18)
	52-60	GVLVHPQWV	213	17/124					
	59-67	WVLTAAHCI	214	15/16					
	54-63	LVHPQWVLTA	215	19/<5		20/<5			A26 (R 16)
	53-62	VLVHPQWVLT	216	17/22					
	54-62	LVHPQWVLT	217			17/n.d.			
55-95	66-73	CIRNKSVI	218					26/20	
	65-73	HCIRNKSVI	219					<15/16	
	56-64	HPQWVLTAA	220				18/<5		
	63-72	AAHCIRNKSV	221	17/<5					

†Scores are given from the two binding prediction programs referenced above (see example 3). R indicates a SYFPEITHI score.

Table 22
PSCA: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	SEQ ID NO	HLA Binding Predictions (SYFPEITHI /NIH)†					
				A*0201	A1	A3	B7	B8	Other
93-123*	116-123	LLWGPGQL	222					16/<5	
	115-123	LLLWGPGQL	223	<15/18					
	114-123	GLLLWGPGQL	224	<15/10					
	99-107	ALQPAAAIL	225	26/9		22/<5	<15/12	16/<5	A26 (R 19)
	98-107	HALQPAAAIL	226	18/<5			<15/12		

*L123 is the C-terminus of the natural protein.
†Scores are given from the two binding prediction programs referenced above (see example 3).

Table 23
Tyrosinase: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	SEQ ID NO	HLA Binding Predictions (SYFPEITHI /NIH)†					
				A*0201	A1	A3	B7	B8	Other
128-157	128-137	APEKDKFFAY	227		29/6		15/<5		B4403 (NIH 14)
	129-137	PEKDKFFAY	228		18/<5			21/<5	
	130-138	EKDKFFAYL	229				15/<5		
	131-138	KDKFFAYL	230					20/<5	
197-228	205-213	PAFLPWHRL	231					15/<5	
	204-213	APAFLPWHRL	232				23/360		
	207-216	FLPWHRLFLL	1	25/1310				<15/8	
	208-216	LPWHRLFLL	9	17/26			20/80	24/16	
	214-223	FLLRWEQEIQ	233			15/<5			
	212-220	RLFLLRWEQ	234			16/<5			
191-211	191-200	GSEIWRDIDF	235		18/68				
	192-200	SEIWRDIDF	236					16/<5	B4403 (NIH 400)
207-230	207-215	FLWHRLFL	8	22/540			<15/6	17/<5	
466-484	473-481	RIWSWLLGA	237	19/13		15/<5			
476-497	476-484	SWLLGAAMV	238	18/<5					
	477-486	WLLGAAMVGA	239	21/194		18/<5			
	478-486	LLGAAMVGA	240	19/19		16/<5			

†Scores are given from the two binding prediction programs referenced above (see example 3).

Table 24
PSMA: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	SEQ ID NO	HLA Binding Predictions (SYFPEITHI /NIH)†					
				A*0201	A1	A3	B7	B8	Other
1-30	4-12	LLHETDSAV	241	25/485		15/<5			
	13-21	ATARRPRWL	242	18/<5				18/<5	A26 (R 19)
53-80	53-61	TPKHNMKAF	243					24/<5	
	64-73	ELKAENIKKF	244			17/<5			A26 (R 30)
	69-77	NIKKFLH[1]NF	245						A26 (R 27)
	68-77	ENIKKFLH[1]NF	246						A26 (R 24)
215-244	220-228	AGAKGVILY	247		25/<5				
457-489	468-477	PLMYSLVHNL	248	22/<5					
	469-477	LMYSLVHNL	249	27/193		<15/9			
	463-471	RVDCTPLMY	250		32/125	25/<5			A26 (R 22)
	465-473	DCTPLMYSL	251						A26 (R 22)
503-533	507-515	SGMPRISKL	252	21/<5				21<5	
	506-515	FSGMPRISKL	253	17/<5					

[1]This H was reported as Y in the SWISSPROT database.
†Scores are given from the two binding prediction programs referenced above (see example 3).

Table 25A
MAGE-1: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	Seq. ID No.	Binding Prediction		
				HLA type	SYFPEITHI	NIH
Mage-1 119-146	125-132	KAEMLESV	256	B5101	19	n.a.
	124-132	TKAEMLESV	257	A0201	20	<5
	123-132	VTKAEMLESV	258	A0201	20	<5
	128-136	MLESVIKNY	259	A1	28	45
				A26	24	n.a.
				A3	17	5
	127-136	EMLESVIKNY	260	A1	15	<1.0
				A26	23	<1.0
	125-133	KAEMLESVI	261	B5101	23	100
				A24	N.A.	4
Mage-1 143-170	146-153	KASESLQL	262	B08	16	<1.0
				B5101	17	N.A.
	145-153	GKASESLQL	263	B2705	17	1
				B2709	16	N.A.
	147-155	ASESLQLVF	264	A1	22	68
	153-161	LVFGIDVKE	265	A26	16	N.A.
				A3	16	<1.0

Table 25B
MAGE-1: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	Seq. ID No.	Binding Prediction		
				HLA type	SYFPEITHI	NIH
Mage-1 99-125	114-121	LLKYRARE	266	B8	25	<1.0
	106-113	VADLVGFL	267	B8	16	<1.0
				B5101	21	N.A.
	105-113	KVADLVGFL	268	A0201	23	44
				A26	25	N.A.
				A3	16	<5
				B0702	14	20
				B2705	14	30
	107-115	ADLVGFLLL	269	A0201	17	<5
				B0702	15	<5
				B2705	16	1
	106-115	VADLVGFLLL	270	A0201	16	<5
				A1	22	3
	114-123	LLKYRAREPV	271	A0201	20	2

Table 26
MAGE-3: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	Seq. ID No.	Binding Prediction		
				HLA type	SYFPEITHI	NIH
Mage-3 267-295	271-278	FLWGPRAL	162	B08	17	<5
	270-278	EFLWGPRAL	163	A26	21	N.A.
				A24	N.A.	30
				B1510	16	N.A.
	271-279	FLWGPRALV	164	A0201	27	2655
				A3	16	2
	278-286	LVETSYVKV	272	A0201	19	<1.0
				A26	17	N.A.
	277-286	ALVETSYVKV	273	A0201	28	428
				A26	16	<5
				A3	18	<5
	285-293	KVLHHMVKI	274	A0201	19	27
				A3	19	<5
	276-284	RALVETSYV	165	A0201	18	20
	283-291	YVKVLHHMV	275	A0201	17	<1.0
	275-283	PRALVETSY	276	A1	17	<1.0
	274-283	GPRALVETSY	277	A1	15	<1.0
	278-287	LVETSYVKVL	278	A0201	18	<1.0
	272-281	LWGPRALVET	168	A0201	16	<1.0
	271-280	FLWGPRALVE	167	A3	22	<5

Table 27A
Fibronectin ED-B: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	Seq. ID No.	Binding Prediction		
				HLA type	SYFPEITHI	NIH
ED-B 14'-21*	4'-5**	*TIIP*EVPQL†	279	A0201	27	7
				A26	28	N.A.
				A3	17	<5
				B8	15	<5
				B1510	15	N.A.
				B2705	17	10
				B2709	15	N.A.
	5'-5**	*DTIIP*EVPQL†	280	A0201	20	<5
				A26	32	N.A.
	1-10	EVPQLTDLSF	281	A26	29	N.A.

*This substrate contains the 14 amino acids from fibronectin flanking ED-B to the N-terminal side.
**These peptides span the junction between the N-terminus of the ED-B domain and the rest of fibronectin.
† The *italicized* lettering indicates sequence outside the ED-B domain.

Table 27B
Fibronectin ED-B: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	Seq. ID No.	Binding Prediction		
				HLA type	SYFPEITHI	NIH
ED-B 8-35	23-30	TPLNSSTI	282	B5101	22	N.A.
	18-25	IGLRWTPL	283	B5101	18	N.A.
	17-25	SIGLRWTPL	284	A0201	20	5
				A26	18	N.A.
				B08	25	<5
	25-33	LNSSTIIGY	285	A1	19	<5
				A26	16	<5
	24-33	PLNSSTIIGY	286	A1	20	<5
				A26	24	N.A.
				A3	16	<5
	23-31	TPLNSSTII	287	B0702	17	8
				B5101	25	440

Table 27C
Fibronectin ED-B: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	Seq. ID No.	Binding Prediction		
				HLA type	SYFPEITHI	NIH
ED-B 20-49	31-38	IGYRITVV	288	B5101	25	N.A.
	30-38	IIGYRITVV	289	A0201	23	15
				A3	17	<1.0
				B08	15	<1.0
				B5101	15	3
	29-38	TIIGYRITVV	290	A0201	26	9
				A26	18	N.A.
				A3	18	<5
	23-30	TPLNSSTI	282	B5101	22	N.A.
	25-33	LNSSTIIGY	285	A1	19	<5
				A26	16	N.A.
	24-33	PLNSSTIIGY	286	A26	24	N.A.
				A3	16	<5
	31-39	IGYRITVVA	291	A3	17	<5
	30-39	IIGYRITVVA	292	A0201	15	<5
				A3	18	<5
	23-31	TPLNSSTII	287	B0702	17	8
				B5101	25	440

Table 28A
CEA: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	Seq. ID No.	Binding Prediction		
				HLA type	SYFPEITHI	NIH
CEA 176-202	184-191	SLPVSPRL	293	B08	19	<5
	183-191	QSLPVSPRL	294	A0201	15	<5
				B1510	15	
				B2705	18	10
				B2709	15	
	186-193	PVSPRLQL	295	B08	18	<5
	185-193	LPVSPRLQL	296	B0702	26	180
				B08	16	<5
				B5101	19	130
	184-193	SLPVSPRLQL	297	A0201	23	21
				A26	18	N.A.
				A3	18	<5
	185-192	LPVSPRLQ	298	B5101	17	N.A.
	192-200	QLSNGNRTL	299	A0201	21	4
				A26	16	N.A.
				A3	19	<5
				B08	17	<5
				B1510	15	
	191-200	LQLSNGNRTL	300	A0201	16	3
	179-187	WVNNQSLPV	301	A0201	16	28
	186-194	PVSPRLQLS	302	A26	17	N.A.
				A3	15	<5

Table 28B
CEA: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	Seq. ID No.	Binding Prediction		
				HLA type	SYFPEITHI	NIH
CEA 354-380	362-369	SLPVSPRL	303	B08	19	<1.0
	361-369	QSLPVSPRL	304	A0201	15	<1.0
				B2705	18	10
				B2709	15	
	364-371	PVSPRLQL	305	B08	18	<1.0
	363-371	LPVSPRLQL	306	B0702	26	180
				B08	16	<1.0
				B5101	19	130
	362-371	SLPVSPRLQL	307	A0201	23	21
				A26	18	N.A.
				A24	N.A.	6
				A3	18	<5
	363-370	LPVSPRLQ	308	B5101	17	N.A.
	370-378	QLSNDNRTL	309	A0201	22	4
				A26	16	N.A.
				A3	17	<1.0
				B08	17	<1.0
	369-378	LQLSNDNRTL	310	A0201	16	3
	357-365	WVNNQSLPV	311	A0201	16	28
	360-368	NQSLPVSPR	312	B2705	14	100

Table 28C
CEA: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	Seq. ID No.	Binding Prediction		
				HLA type	SYFPEITHI	NIH
CEA 532-558	540-547	SLPVSPRL	313	B08	19	<5
	539-547	QSLPVSPRL	314	A0201	15	<5
				B1510	15	<5
				B2705	18	10
				B2709	15	
	542-549	PVSPRLQL	315	B08	18	<5
	541-549	LPVSPRLQL	316	B0702	26	180
				B08	16	<1.0
				B5101	19	130
	540-549	SLPVSPRLQL	317	A0201	23	21
				A26	18	N.A.
				A3	18	<5
	541-548	LPVSPRLQ	318	B5101	17	N.A.
	548-556	QLSNGNRTL	319	A0201	24	4
				A26	16	N.A.
				A3	19	<1.0
				B08	17	<1.0
				B1510	15	
	547-556	LQLSNGNRTL	320	A0201	16	3
	535-543	WVNGQSLPV	321	A0201	18	28
				A3	15	<1.0
	533-541	LWWVNGQSL	322	A0201	15	<5

Table 28D
CEA: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	Seq. ID No.	Binding Prediction		
				HLA type	SYFPEITHI	NIH
CEA 532-558 (continued)	532-541	YLWWVNGQSL	323	A0201	25	816
				A26	18	N.A.
	538-546	GQSLPVSPR	324	B2705	17	100

Table 29A
HER2/NEU: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	Seq. ID No.	Binding Prediction		
				HLA type	SYFPEITHI	NIH
Her-2 25-52	30-37	DMKLRLPA	325	B08	19	8
	28-37	GTDMKLRLPA	326	A1	23	6
	42-49	HLDMLRHL	327	B08	17	<5
	41-49	THLDMLRHL	328	A0201	17	<5
				B1510	24	N.A.
	40-49	ETHLDMLRHL	329	A26	29	N.A.
	36-43	PASPETHL	330	B5101	17	N.A.
	35-43	LPASPETHL	331	A0201	15	<5
				B5101	20	130
				B5102	N.A.	100
	34-43	RLPASPETHL	332	A0201	20	21
	38-46	SPETHLDML	333	A0201	15	<5
				B0702	20	24
				B08	18	<5
				B5101	18	110
	37-46	ASPETHLDML	334	A0201	18	<5
	42-50	HLDMLRHLY	335	A1	29	25
				A26	20	N.A.
				A3	17	4
	41-50	THLDMLRHLY	336	A1	18	<1.0

Table 29B
HER2/NEU: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	Seq. ID No.	Binding Prediction		
				HLA type	SYFPEITHI	NIH
Her-2 705-732	719-726	ELRKVKVL	337	B08	24	16
	718-726	TELRKVKVL	338	A0201	16	1
				B08	22	<5
				B5101	16	<5
	717-726	ETELRKVKVL	339	A1	18	2
				A26	28	6
	715-723	LKETELRKV	340	A0201	17	<5
				B5101	15	<5
	714-723	ILKETELRKV	341	A0201	29	8
	712-720	MRILKETEL	342	A0201	15	<5
				B08	22	<5
				B2705	27	2000
				B2709	21	N.A.
	711-720	QMRILKETEL	343	A0201	20	2
				B0702	13	40
	717-725	ETELRKVKV	344	A1	18	5
				A26	18	N.A.
	716-725	KETELRKVKV	345	A0201	16	19
	706-714	MPNQAQMRI	346	B0702	16	8
				B5101	22	629
	705-714	AMPNQAQMRI	347	A0201	18	8
	706-715	MPNQAQMRIL	348	B0702	20	80

Table 29C
HER2/NEU: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	Seq. ID No.	Binding Prediction		
				HLA type	SYFPEITHI	NIH
Her-2 954-982	966-973	RPRFRELV	349	B08	20	24
				B5101	18	N.A.
	965-973	CRPRFRELV	350	B2709	18	
	968-976	RFRELVSEF	351	A26	25	N.A.
				A24	N.A.	32
				A3	15	<5
				B08	16	<5
				B2705	19	
	967-976	PRFRELVSEF	352	A26	18	N.A.
	964-972	ECRPRFREL	353	A26	21	N.A.
				A24	N.A.	6
				B0702	15	40
				B8	27	640
				B1510	16	<5

Table 30
NY-ESO-1: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	Seq. ID No.	Binding Prediction		
				HLA type	SYFPEITHI	NIH
NY-ESO-1 51-77	67-75	GAASGLNGC	354	A0201	15	<5
	52-60	RASGPGGGA	355	B0702	15	<5
	64-72	PHGGAASGL	356	B1510	21	N.A.
	63-72	GPHGGAASGL	357	B0702	22	80
	60-69	APRGPHGGAA	358	B0702	23	60

Table 31A
PRAME: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	Seq. ID No.	Binding Prediction		
				HLA type	SYFPEITHI	NIH
PRAME 103-135	112-119	VRPRRWKL	359	B08	19	
	111-119	EVRPRRWKL	360	A26	27	N.A.
				A24	N.A.	5
				A3	19	N.A.
				B0702	15	(B7) 300.00
				B08	26	160
	113-121	RPRRWKLQV	361	B0702	21	(B7) 40.00
				B5101	19	110
	114-122	PRRWKLQVL	362	B08	26	<5
				B2705	23	200
	113-122	RPRRWKLQVL	363	B0702	24	(B7) 800.00
				B8	N.A.	160
				B5101	N.A.	61
				B5102	N.A.	61
				A24	N.A.	10
	116-124	RWKLQVLDL	364	B08	22	<5
				B2705	17	3
	115-124	RRWKLQVLDL	365	A0201	16	<5
PRAME 161-187	174-182	PVEVLVDLF	366	A26	25	N.A.

Table 31B

PRAME: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	Seq. ID No.	Binding Prediction		
				HLA type	SYFPEITHI	NIH
PRAME 185-215	199-206	VKRKKNVL	367	B08	27	8
	198-206	KVKRKKNVL	368	A0201	16	<1.0
				A26	20	N.A.
				A3	22	<1.0
				B08	30	40
				B2705	16	
	197-206	EKVKRKKNVL	369	A26	15	N.A.
	198-205	KVKRKKNV	370	B08	20	6
	201-208	RKKNVLRL	371	B08	20	<5
	200-208	KRKKNVLRL	372	A0201	15	<1.0
				A26	15	N.A.
				B0702	15	<1.0
				B08	21	<1.0
				B2705	28	
				B2709	25	
	199-208	VKRKKNVLRL	373	A0201	16	<1.0
				B0702	16	4
	189-196	DELFSYLI	374	B5101	15	N.A.
	205-213	VLRLCCKKL	375	A0201	22	3
				A26	17	N.A.
				B08	25	8
	204-213	NVLRLCCKKL	376	A0201	17	7
				A26	19	N.A.

Table 31C
PRAME: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	Seq. ID No.	Binding Prediction		
				HLA type	SYFPEITHI	NIH
PRAME 185-215 (continued)	194-202	YLIEKVKRK	377	A0201	20	<1.0
				A26	18	N.A.
				A3	25	68
				B08	20	<1.0
				B2705	17	
PRAME 71-98	74-81	QAWPFTCL	378	B5101	17	n.a.
	73-81	VQAWPFTCL	379	A0201	14	7
				A24	n.a.	5
				B0702	16	6
	72-81	MVQAWPFTCL	380	A26	22	n.a.
				A24	n.a.	7
				B0702	13	30
	81-88	LPLGVLMK	381	B5101	18	n.a.
	80-88	CLPLGVLMK	382	A0201	17	<1.0
				A3	27	120
	79-88	TCLPLGVLMK	383	A1	12	10
				A3	19	3
	84-92	GVLMKGQHL	384	A0201	18	7
				A26	21	n.a.
				B08	21	4
	81-89	LPLGVLMKG	385	B5101	20	2
	80-89	CLPLGVLMKG	386	A0201	16	<1.0
	76-85	WPFTCLPLGV	387	B0702	18	4

Table 31D
PRAME: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	Seq. ID No.	Binding Prediction		
				HLA type	SYFPEITHI	NIH
PRAME 39-65	51-59	ELFPPLFMA	388	A0201	19	18
				A26	23	N.A.
	49-57	PRELFPPLF	389	B2705	22	
				B2709	19	
	48-57	LPRELFPPLF	390	B0702	19	4
	50-58	RELFPPLFM	391	B2705	16	
				B2705	15	
	49-58	PRELFPPLFM	392	A1	16	<1.0

Table 32
PSA: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	Seq. ID No.	Binding Prediction		
				HLA type	SYFPEITHI	NIH
PSA 232-258	239-246	RPSLYTKV	393	B5101	21	N.A.
	238-246	ERPSLYTKV	394	B2705	15	60
	236-243	LPERPSLY	395	B5101	18	N.A.
	235-243	ALPERPSLY	396	A1	19	<1.0
				A26	22	N.A.
				A3	26	6
				B08	16	<1.0
				B2705	11	15
				B2709	19	N.A.
	241-249	SLYTKVVHY	397	A0201	20	<1.0
				A1	19	<1.0
				A26	25	N.A.
				A3	26	60
				B08	20	<1.0
				B2705	13	75
	240-249	PSLYTKVVHY	398	A1	20	<1.0
				A26	16	N.A.
	239-247	RPSLYTKVV	399	B0702	21	4
				B5101	23	110

Table 33A
PSMA: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	Seq. ID No.	Binding Prediction		
				HLA type	SYFPEITHI	NIH
PSMA 202-228	211-218	GNKVKNAQ	400	B08	22	<5
	202-209	IARYGKVF	401	B08	18	<5
	217-225	AQLAGAKGV	402	A0201	16	26
	207-215	KVFRGNKVK	403	A3	32	15
	211-219	GNKVKNAQL	404	B8	33	80
				B2705	17	20
PSMA 255-282	269-277	TPGYPANEY	405	A1	16	<5
	268-277	LTPGYPANEY	406	A1	21	1
				A26	24	N.A.
	271-279	GYPANEYAY	407	A1	15	<5
	270-279	PGYPANEYAY	408	A1	19	<5
	266-274	DPLTPGYPA	409	B0702	21	3
				B5101	17	20
PSMA 483-509	492-500	SLYESWTKK	410	A0201	17	<5
				A3	27	150
				B2705	18	150
	491-500	KSLYESWTKK	411	A3	16	<5
	486-494	EGFEGKSLY	412	A1	19	<5
				A26	21	N.A.
				B2705	16	<5
	485-494	DEGFEGKSLY	413	A1	17	<5
				A26	17	N.A.
	498-506	TKKSPSPEF	414	B08	17	<5

Table 33B
PSMA: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	Seq. ID No.	Binding Prediction		
				HLA type	SYFPEITHI	NIH
PSMA 483-509 (continued)	497-506	WTKKSPSPEF	415	A26	24	N.A.
	492-501	SLYESWTKKS	416	A0201	16	<5
				A3	16	<5
PSMA 721-749	725-732	WGEVKRQI	417	B08	17	<5
				B5101	17	N.A.
	724-732	AWGEVKRQI	418	B5101	15	6
	723-732	KAWGEVKRQI	419	A0201	16	<1.0
	723-730	KAWGEVKR	420	B5101	15	N.A.
	722-730	SKAWGEVKR	421	B2705	15	<5
	731-739	QIYVAAFTV	422	A0201	21	177
				A3	21	<1.0
				B5101	15	5
	733-741	YVAAFTVQA	423	A0201	17	6
				A3	20	<1.0
	725-733	WGEVKRQIY	424	A1	26	11
	727-735	EVKRQIYVA	425	A26	22	N.A.
				A3	18	<1.0
	738-746	TVQAAAETL	426	A26	18	N.A.
				A3	19	<1.0
	737-746	FTVQAAAETL	427	A0201	17	<1.0
				A26	19	N.A.

Table 33C
PSMA: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	Seq. ID No.	Binding Prediction		
				HLA type	SYFPEITHI	NIH
PSMA 721-749 (continued)	729-737	KRQIYVAAF	428	A26	16	N.A.
				B2705	24	3000
				B2709	21	N.A.
	721-729	PSKAWGEVK	429	A3	20	<1.0
	723-731	KAWGEVKRQ	430	B5101	16	<1.0
PSMA 95-122	100-108	WKEFGLDSV	431	A0201	16	<5
	99-108	QWKEFGLDSV	432	A0201	17	<5
	102-111	EFGLDSVELA	433	A26	16	N.A.

Table 34A
SCP-1: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	Seq. ID No.	Binding Prediction		
				HLA type	SYFPEITHI	NIH
SCP-1 117-143	126-134	ELRQKESKL	434	A0201	20	<5
				A26	26	N.A.
				A3	17	<5
				B0702	13	(B7) 40.00
				B8	34	320
	125-134	AELRQKESKL	435	A0201	16	<5
	133-141	KLQENRKII	436	A0201	20	61
SCP-1 281-308	298-305	QLEEKTKL	437	B08	28	2
	297-305	NQLEEKTKL	438	A0201	16	33
				B2705	19	200
	288-296	LLEESRDKV	439	A0201	25	15
				B5101	15	3
	287-296	FLLEESRDKV	440	A0201	27	2378
	291-299	ESRDKVNQL	441	A26	21	N.A.
				B08	29	240
	290-299	EESRDKVNQL	442	A26	19	N.A.
SCP-1 471-498	475-483	EKEVHDLEY	443	A1	31	11
				A26	17	N.A.
	474-483	REKEVHDLEY	444	A1	21	<1.0
	480-488	DLEYSYCHY	445	A1	26	45
				A26	30	N.A.
				A3	16	<5
	477-485	EVHDLEYSY	446	A1	15	1

Table 34B
SCP-1: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	Seq. ID No.	Binding Prediction		
				HLA type	SYFPEITHI	NIH
SCP-1 471-498 (continued)	477-485	EVHDLEYSY		A26	29	N.A.
				A3	19	<1.0
	477-486	EVHDLEYSYC	447	A26	22	N.A.
SCP-1 493-520	502-509	KLSSKREL	448	B08	26	4
	508-515	ELKNTEYF	449	B08	24	<1.0
	507-515	RELKNTEYF	450	B2705	18	45
				B4403	N.A.	120
	496-503	KRGQRPKL	451	B08	18	<1.0
	494-503	LPKRGQRPKL	452	B0702	22	120
				B8	N.A.	16
				B5101	N.A.	130
				B3501	N.A.	60
	509-517	LKNTEYFTL	453	A0201	15	<5
	508-517	ELKNTEYFTL	454	A0201	18	<1.0
				A26	27	N.A.
				A3	16	<1.0
	506-514	KRELKNTEY	455	A1	26	2
				B2705	26	3000
	502-510	KLSSKRELK	456	A3	25	60
	498-506	GQRPKLSSK	457	A3	22	4
				B2705	18	200
	497-506	RGQRPKLSSK	458	A3	22	<1.0
	500-508	RPKLSSKRE	459	B08	18	<1.0

Table 34C
SCP-1: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	Seq. ID No.	Binding Prediction		
				HLA type	SYFPEITHI	NIH
SCP-1 570-596	573-580	LEYVREEL	460	B08	19	<5
	572-580	ELEYVREEL	461	A0201	17	<1.0
				A26	23	N.A.
				A24	N.A.	9
				B08	20	N.A.
	571-580	N ELEYVREEL	462	A0201	16	4
	579-587	ELKQKRDEV	463	A0201	19	<1.0
				A26	18	N.A.
				B08	29	48
	575-583	YVREELKQK	464	A26	17	N.A.
				A3	27	2
SCP-1 618-645	632-640	QLNVYEIKV	465	A0201	24	70
	630-638	SKQLNVYEI	466	A0201	17	<5
	628-636	AESKQLNVY	467	A1	19	<5
				A26	16	N.A.
	627-636	TAESKQLNVY	468	A1	26	45
				A26	15	N.A.

Table 34D
SCP-1: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	Seq. ID No.	Binding Prediction		
				HLA type	SYFPEITHI	NIH
SCP-1 633-660	638-645	IKVNKLEL	469	B08	21	<1.0
	637-645	EIKVNKLEL	470	A0201	17	<1.0
				A26	26	N.A.
				B08	28	8
				B1510	15	N.A.
	636-645	YEIKVNKLEL	471	A0201	17	2
	642-650	KLELELESA	472	A0201	20	1
				A3	16	<1.0
	635-643	VYEIKVNKL	473	A0201	18	<1.0
				A24	N.A.	396
				B08	22	<1.0
	634-643	NVYEIKVNKL	474	A0201	24	56
				A26	25	N.A.
				A24	N.A.	6
				A3	15	<5
				B0702	11	(B7) 20
				B08	N.A.	6
	646-654	ELESAKQKF	475	A26	27	N.A.
SCP-1 640-668	642-650	KLELELESA	476	A0201	20	1
				A3	16	<1.0
	646-654	ELESAKQKF	477	A26	27	N.A.

Table 34E
SCP-1: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	Seq. ID No.	Binding Prediction		
				HLA type	SYFPEITHI	NIH
SCP-1 768-796	771-778	KEKLKREA	478	B08	21	<5
	777-785	EAKENTATL	479	A0201	18	<5
				A26	18	N.A.
				A24	N.A.	5
				B0702	13	12
				B08	28	48
				B5101	20	121
	776-785	REAKENTATL	480	A0201	16	<5
	773-782	KLKREAKENT	481	A3	17	<5
SCP-1 92-125	112-119	EAEKIKKW	482	B5101	17	N.A.
	101-109	GLSRVYSKL	483	A0201	23	32
				A26	22	N.A
				A24	N.A.	6
				A3	17	3
				B08	17	<1.0
	100-109	EGLSRVYSKL	484	A26	21	N.A.
				A24	N.A.	9
	108-116	KLYKEAEKI	485	A0201	22	57
				A3	20	9
				B5101	18	5
	98-106	NSEGLSRVY	486	A1	31	68
	97-106	ENSEGLSRVY	487	A26	18	N.A.
	102-110	LSRVYSKLY	488	A1	22	<1.0

Table 34F
SCP-1: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	Seq. ID No.	Binding Prediction		
				HLA type	SYFPEITHI	NIH
SCP-1 92-125 (continued)	101-110	GLSRVYSKLY	489	A1	18	<1.0
				A26	18	N.A.
				A3	19	18
	96-105	LENSEGLSRV	490	A0201	17	5
	108-117	KLYKEAEKIK	491	A3	27	150
SCP-1 931-958	949-956	REDRWAVI	492	B5101	15	N.A.
	948-956	MREDRWAVI	493	B2705	18	600
				B2709	18	N.A.
				B5101	15	1
	947-956	KMREDRWAVI	494	A0201	21	6
				B08	N.A.	15
	947-955	KMREDRWAV	495	A0201	22	411
	934-942	TTPGSTLKF	496	A26	25	N.A.
	933-942	LTTPGSTLKF	497	A26	23	N.A.
	937-945	GSTLKFGAI	498	B08	19	1
	945-953	IRKMREDRW	499	B08	19	<5
SCP-1 232-259	236-243	RLEMHFKL	500	B08	16	<5
	235-243	SRLEMHFKL	501	A0201	18	<5
				B2705	25	2000
				B2709	22	
	242-250	KLKEDYEKI	502	A0201	22	4

Table 34G
SCP-1: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	Seq. ID No.	Binding Prediction		
				HLA type	SYFPEITHI	NIH
SCP-1 232-259 (continued)				A26	16	N.A.
				A3	15	3
				B08	24	<5
				B5101	14	2
	249-257	KIQHLEQEY	503	A1	15	<5
				A26	23	N.A.
				A3	17	<5
	248-257	EKIQHLEQEY	504	A1	15	<5
				A26	21	N.A.
	233-242	ENSRLEMHF	505	A26	19	N.A.
	236-245	RLEMHFKLKE	506	A1	19	<5
				A3	17	<5
SCP-1 310-340	324-331	LEDIKVSL	507	B08	20	<1.0
	323-331	ELEDIKVSL	508	A0201	21	<1.0
				A26	25	N.A.
				A24	N.A.	10
				A3	17	<1.0
				B08	19	<1.0
				B1510	16	N.A.
	322-331	KELEDIKVSL	509	A0201	19	22
	320-327	LTKELEDI	500	B08	18	<5
	319-327	HLTKELEDI	511	A0201	21	<1.0
	330-338	SLQRSVSTQ	512	A0201	18	<1.0

Table 34H
SCP-1: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	Seq. ID No.	Binding Prediction		
				HLA type	SYFPEITHI	NIH
SCP-1 310-340 (continued)	321-329	TKELEDIKV	513	A1	16	<1.0
	320-329	LTKELEDIKV	514	A0201	19	<1.0
	326-335	DIKVSLQRSV	515	A26	18	N.A.
SCP-1 272-305	281-288	KMKDLTFL	516	B08	20	3
	280-288	NKMKDLTFL	517	A0201	15	1
	279-288	ENKMKDLTFL	518	A26	19	N.A.
	288-296	LLEESRDKV	519	A0201	25	15
				B5101	15	3
	287-296	FLLEESRDKV	520	A0201	27	2378
	291-299	ESRDKVNQL	521	A26	21	N.A.
				B08	29	240
	290-299	EESRDKVNQL	522	A26	19	N.A.
	277-285	EKENKMKDL	523	A26	19	N.A.
				B08	23	<1.0
	276-285	TEKENKMKDL	524	A26	15	N.A.
	279-287	ENKMKDLTF	525	A26	18	N.A.
				B08	28	4
SCP-1 211-239	218-225	IEKMITAF	526	B08	17	<5
	217-225	NIEKMITAF	527	A26	26	N.A.
	216-225	SNIEKMITAF	528	A26	19	N.A.
	223-230	TAFEELRV	529	B5101	23	N.A.
	222-230	ITAFEELRV	530	A0201	18	2
	221-230	MITAFEELRV	531	A0201	18	16

Table 34I
SCP-1: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	Seq. ID No.	Binding Prediction		
				HLA type	SYFPEITHI	NIH
SCP-1 211-239 (contimued)	220-228	KMITAFEEL	532	A0201	23	50
				A26	15	N.A.
				A24	N.A.	16
	219-228	EKMITAFEEL	533	A26	19	N.A.
	227-235	ELRVQAENS	534	A3	16	<1.0
				B08	15	<1.0
	213-222	DLNSNIEKMI	535	A0201	17	<1.0
				A26	16	N.A.
SCP-1 836-863	837-844	WTSAKNTL	536	B08	20	4
	846-854	TPLPKAYTV	537	A0201	18	2
				B0702	17	4
				B08	16	2
				B5101	25	220
	845-854	STPLPKAYTV	538	A0201	19	<5
	844-852	LSTPLPKAY	539	A1	23	8
	843-852	TLSTPLPKAY	540	A1	16	<1.0
				A26	19	N.A.
				A3	18	2
	842-850	NTLSTPLPK	541	A3	16	3
	841-850	KNTLSTPLPK	542	A3	18	<1.0

Table 34J
SCP-1: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	Seq. ID No.	Binding Prediction		
				HLA type	SYFPEITHI	NIH
SCP-1 819-845	828-835	ISKDKRDY	543	B08	21	3
				A26	21	N.A.
	826-835	HGISKDKRDY	544	A1	15	<5
	832-840	KRDYLWTSA	545	B2705	16	600
	829-838	SKDKRDYLWT	546	A1	18	<5
SCP-1 260-288	279-286	ENKMKDLT	547	B08	22	8
	260-268	EINDKEKQV	548	A0201	17	3
				A26	19	N.A.
				B08	17	<5
	274-282	QITEKENKM	549	A0201	17	3
				A26	22	N.A.
				B08	16	<5
	269-277	SLLLIQITE	550	A0201	16	<1.0
				A3	18	<1.0
SCP-1 437-464	453-460	FEKIAEEL	551	B08	21	<1.0
	452-460	QFEKIAEEL	552	B2705	15	
	451-460	KQFEKIAEEL	553	A0201	16	56
	449-456	DNKQFEKI	554	B08	16	2
				B5101	16	N.A.
	448-456	YDNKQFEKI	555	B5101	16	1
	447-456	LYDNKQFEKI	556	A1	15	<1.0

Table 34K
SCP-1: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	Seq. ID No.	Binding Prediction		
				HLA type	SYFPEITHI	NIH
SCP-1 437-464 (continued)	440-447	LGEKETLL	557	B5101	16	N.A.
	439-447	VLGEKETLL	558	A0201	24	149
				A26	19	N.A.
				B08	29	12
	438-447	KVLGEKETLL	559	A0201	19	24
				A26	20	N.A.
				A24	N.A.	12
				A3	18	<1.0
				B0702	14	20
SCP-1 383-412	390-398	LLRTEQQRL	560	A0201	22	3
				A26	18	N.A.
				B08	22	1.6
				B2705	15	30
	389-398	ELLRTEQQRL	561	A0201	19	6
				A26	24	N.A.
				A3	15	<1.0
	393-401	TEQQRLENY	562	A1	15	<5
				A26	16	N.A.
	392-401	RTEQQRLENY	563	A1	31	113
				A26	26	N.A.
	402-410	EDQLIILTM	564	A26	18	N.A.
	397-406	RLENYEDQLI	565	A0201	17	<1.0
				A3	15	<1.0

Table 34L
SCP-1: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	Seq. ID No.	Binding Prediction		
				HLA type	SYFPEITHI	NIH
SCP-1 366-394	368-375	KARAAHSF	566	B08	16	<1.0
	376-384	VVTEFETTV	567	A0201	19	161
				A3	16	<1.0
	375-384	FVVTEFETTV	568	A0201	17	106
	377-385	VTEFETTVC	569	A1	18	2
	376-385	VVTEFETTVC	570	A3	16	<5
SCP-1 331-357	344-352	DLQIATNTI	571	A0201	22	<5
				A3	15	<1.0
				B5101	17	11
	347-355	IATNTICQL	572	A0201	19	1
				B08	16	<1.0
				B5101	20	79
	346-355	QIATNTICQL	573	A0201	24	7
				A26	24	N.A.

Table 35
SSX-4: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	Seq. ID No.	Binding Prediction		
				HLA type	SYFPEITHI	NIH
SSX4 45-76	57-65	VMTKLGFKV	574	A0201	21	495
	53-61	LNYEVMTKL	575	A0201	17	7
	52-61	KLNYEVMTKL	576	A0201	23	172
				A26	21	N.A.
				A24	N.A.	18
				A3	14	4
				B7	N.A.	4
	66-74	TLPPFMRSK	577	A26	16	N.A.
				A3	25	14
SSX4 98-124	110-118	KIMPKKPAE	578	A0201	15	<5
				A26	15	N.A.
				A3	16	<5
	103-112	SLQRIFPKIM	579	A0201	15	8
				A26	16	N.A.
				A3	15	<5

Table 36
Tyrosinase: Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Substrate	Epitope	Sequence	Seq. ID No.	Binding Prediction		
				HLA type	SYFPEITHI	NIH
Tyr 445-474	463-471	YIKSYLEQA	580	A0201	18	<5
				A26	17	N.A.
	459-467	SFQDYIKSY	581	A1	18	<5
				A26	22	N.A.
	458-467	DSFQDYIKSY	582	A1	19	<5
				A26	24	N.A.
Tyr 490-518	507-514	LPEEKQPL	583	B08	28	5
				B5101	18	N.A.
	506-514	QLPEEKQPL	584	A0201	22	88
				A26	20	N.A.
				A24	N.A.	9
				B08	18	<5
	505-514	KQLPEEKQPL	585	A0201	15	28
				A24	N.A.	17
	507-515	LPEEKQPLL	586	A0201	15	<5
				B0702	21	24
				B08	28	5
				B5101	21	157
	506-515	QLPEEKQPLL	587	A0201	23	88
				A26	20	N.A.
				A24	N.A.	7
	497-505	SLLCRHKRK	588	A3	25	15

Example 15

Evaluating Likelihood of Epitope Cross-reactivity on Non-target Tissues.

As noted above PSA is a member of the kallikrein family of proteases, which is itself a subset of the serine protease family. While the members of this family sharing the greatest degree of sequence identity with PSA also share similar expression profiles, it remains possible that individual epitope sequences might be shared with proteins having distinctly different expression profiles. A first step in evaluating the likelihood of undesirable cross-reactivity is the identification of shared sequences. One way to accomplish this is to conduct a BLAST search of an epitope sequence against the SWISSPROT or Entrez non-redundant peptide sequence databases using the "Search for short nearly exact matches" option; hypertext transfer protocol accessible on the world wide web (http://www) at "ncbi.nlm.nih.gov/blast/index.html". Thus searching SEQ ID NO. 214, WVLTAAHCI, against SWISSPROT (limited to entries for homo sapiens) one finds four exact matches, including PSA. The other three are from kallikrein 1 (tissue kallikrein), and elastase 2A and 2B. While these nine amino acid segments are identical, the flanking sequences are quite distinct, particularly on the C-terminal side, suggesting that processing may proceed differently and that thus the same epitope may not be liberated from these other proteins. (Please note that kallikrein naming is confused. Thus the kallikrein 1 [accession number P06870] is a different protein than the one [accession number AAD13817] mentioned in the paragraph on PSA above in the section on tumor-associated antigens).

It is possible to test this possibility in several ways. Synthetic peptides containing the epitope sequence embedded in the context of each of these proteins can be subjected to *in vitro* proteasomal digestion and analysis as described above. Alternatively, cells expressing these other proteins, whether by natural or recombinant expression, can be used as targets in a cytotoxicity (or similar) assay using $CD8^+$ T cells that recognize the epitope, in order to determine if the epitope is processed and presented.

Example 16

Epitope Clusters.

Known and predicted epitopes are generally not evenly distributed across the sequences of protein antigens. As referred to above, we have defined segments of sequence containing a higher than average density of (known or predicted) epitopes as epitope clusters. Among the uses of epitope clusters is the incorporation of their sequence into substrate peptides used in proteasomal digestion analysis as described herein. Epitope clusters can also be useful as vaccine components. A fuller discussion of the definition and uses of epitope clusters is found in U.S. Patent Application No. 09/561,571 entitled EPITOPE CLUSTERS.

The following tables (37-60) present 9-mer epitopes predicted for HLA-A2 binding using both the SYFPEITHI and NIH algorithms and the epitope density of regions of overlapping epitopes, and of epitopes in the whole protein, and the ratio of these two densities. (The ratio must exceed one for there to be a cluster by the above definition; requiring higher values of this ratio reflect preferred embodiments). Individual 9-mers are ranked by score and identified by the position of their first amino in the complete protein sequence. Each potential cluster from a protein is numbered. The range of amino acid positions within the complete sequence that the cluster covers is indicated as are the rankings of the individual predicted epitopes it is made up of.

Table 37
BIMAS-NIH/Parker algorithm Results for gp100

Rank	Start	Score	Rank	Start	Score
1	619	1493	21	416	19
2	602	413	22	25	18
3	162	226	23	566	17
4	18	118	24	603	15
5	178	118	25	384	14
6	273	117	26	13	14
7	601	81	27	290	12
8	243	63	28	637	10
9	606	60	29	639	9
10	373	50	30	485	9
11	544	36	31	453	8
12	291	29	32	102	8
13	592	29	33	399	8
14	268	29	34	456	7
15	47	27	35	113	7
16	585	26	36	622	7
17	576	21	37	69	7
18	465	21	38	604	6
19	570	20	39	350	6
20	9	19	40	583	5

Table 38
SYFPEITHI (Rammensee algorithm) Results for gp100

Rank	Start	Score	Rank	Start	Score	Rank	Start	Score
1	606	30	37	291	20	73	60	18
2	162	29	38	269	20	74	17	18
3	456	28	39	2	20	75	613	17
4	18	28	40	610	19	76	599	17
5	602	27	41	594	19	77	572	17
6	598	27	42	591	19	78	557	17
7	601	26	43	583	19	79	556	17
8	597	26	44	570	19	80	512	17
9	13	26	45	488	19	81	406	17
10	585	25	46	446	19	82	324	17
11	449	25	47	322	19	83	290	17
12	4	25	48	267	19	84	101	17
13	603	24	49	250	19	85	95	17
14	576	24	50	205	19	86	635	16
15	453	24	51	180	19	87	588	16
16	178	24	52	169	19	88	584	16
17	171	24	53	88	19	89	577	16
18	11	24	54	47	19	90	559	16
19	619	23	55	10	19	91	539	16
20	280	23	56	648	18	92	494	16
21	268	23	57	605	18	93	482	16
22	592	22	58	604	18	94	468	16
23	544	22	59	595	18	95	442	16
24	465	22	60	571	18	96	413	16
25	399	22	61	569	18	97	408	16
26	373	22	62	450	18	98	402	16
27	273	22	63	409	18	99	286	16
28	243	22	64	400	18	100	234	16
29	566	21	65	371	18	101	217	16
30	563	21	66	343	18	102	211	16
31	485	21	67	298	18	103	176	16
32	384	21	68	209	18	104	107	16
33	350	21	69	102	18	105	96	16
34	9	21	70	97	18	106	80	16
35	463	20	71	76	18	107	16	16
36	397	20	72	69	18	108	14	16
						109	7	16

Table 39

Prediction of clusters for gp100
Total AAs: 661
Total 9-mers: 653
SYFPEITHI 16: 109 9-mers
NIH 5: 40 9-mers

	Cluster #	AAs	Epitopes (by Rank)	Epitopes/AA Cluster	Whole Pr	Ratio
SYFPEITHI	1	2 to 26	39, 12, 109, 34, 55, 11, 9, 108, 107, 74, 4	0.440	0.165	2.668
	2	69-115	72, 71, 106, 53, 85, 105, 70, 84, 69, 104	0.213	0.165	1.290
	3	95-115	85, 105, 70, 84, 69	0.238	0.165	1.444
	4	162-188	2, 52, 17, 103, 16, 51	0.222	0.165	1.348
	5	205-225	50, 68, 102, 101	0.190	0.165	1.155
	6	243-258	28, 49	0.125	0.165	0.758
	7	267-306	48, 21, 38, 27, 20, 99, 83, 37, 67	0.225	0.165	1.364
	8	322-332	47, 82	0.182	0.165	1.103
	9	343-358	66, 33	0.125	0.165	0.758
	10	371-381	65, 26	0.182	0.165	1.103
	11	397-421	36, 25, 64, 98, 81, 97, 63, 96	0.320	0.165	1.941
	12	442-476	95, 46, 11, 62, 15, 3, 35, 24, 94	0.257	0.165	1.559
	13	482-502	93, 31, 45, 93	0.190	0.165	1.155
	14	539-552	91, 23	0.143	0.165	0.866
	15	556-627	79, 78, 90, 30, 29, 61, 44, 60, 77, 14, 89, 43, 88, 10, 87, 42, 22, 41, 59, 8, 6, 76, 7, 5, 13, 58, 57, 1, 40, 75, 19	0.431	0.165	2.611
NIH						
	1	9 to 33	20, 26, 4, 22	0.160	0.061	2.644
	2	268-281	14, 6	0.143	0.061	2.361
	3	290-299	27, 12	0.200	0.061	3.305
	4*	102-121	32, 35	0.100	0.061	1.653
	5*	373-392	10, 25	0.100	0.061	1.653
	6	453-473	31, 34, 18	0.143	0.061	2.361
	7	566-600	23, 19, 17, 40, 16, 13	0.171	0.061	2.833
	8	601-614	7, 2, 24, 38, 9	0.357	0.061	5.902
	9	619-630	1, 36	0.17	0.061	2.754
	10	637-647	28, 29	0.18	0.061	3.005

*Nearby but not overlapping epitopes

Table 40

BIMAS-NIH/Parker algorithm Results for PSMA

Rank	Start	Score
1	663	1360
2	711	1055
3	4	485
4	27	400
5	26	375
6	668	261
7	707	251
8	469	193
9	731	177
10	35	67
11	33	64
12	554	59
13	427	50
14	115	47
15	20	40
16	217	26
17	583	24
18	415	19
19	193	14
20	240	12
21	627	11
22	260	10
23	130	10
24	741	9
25	3	9
26	733	8
27	726	7
28	286	6
29	174	5
30	700	5

Table 41
SYFPEITHI (Rammensee algorithm) Results for PSMA

Rank	Start	Score	Rank	Start	Score	Rank	Start	Score
1	469	27	31	26	20	61	305	17
2	27	27	32	3	20	62	304	17
3	741	26	33	583	19	63	286	17
4	711	26	34	579	19	64	282	17
5	354	25	35	554	19	65	169	17
6	4	25	36	550	19	66	142	17
7	663	24	37	547	19	67	122	17
8	130	24	38	390	19	68	738	16
9	57	24	39	219	19	69	634	16
10	707	23	40	193	19	70	631	16
11	260	23	41	700	18	71	515	16
12	20	23	42	472	18	72	456	16
13	603	22	43	364	18	73	440	16
14	218	22	44	317	18	74	385	16
15	109	22	45	253	18	75	373	16
16	731	21	46	91	18	76	365	16
17	668	21	47	61	18	77	361	16
18	660	21	48	13	18	78	289	16
19	507	21	49	733	17	79	278	16
20	454	21	50	673	17	80	258	16
21	427	21	51	671	17	81	247	16
22	358	21	52	642	17	82	217	16
23	284	21	53	571	17	83	107	16
24	115	21	54	492	17	84	100	16
25	33	21	55	442	17	85	75	16
26	606	20	56	441	17	86	37	16
27	568	20	57	397	17	87	30	16
28	473	20	58	391	17	88	21	16
29	461	20	59	357	17			
30	200	20	60	344	17			

Table 42

Prediction of clusters for prostate-specific membrane antigen (PSMA)

Total AAs: 750
Total 9-mers: 742
SYFPEITHI 16: 88 9-mers
NIH 5: 30 9-mers

				Epitopes/AA		
	Cluster #	Aas	Epitopes (by rank)	Cluster	Whole Pr	Ratio
SYFPEITHI	1	3 to 12	32, 6	0.200	0.117	1.705
	2	13-45	13, 12, 88, 31, 2, 87, 25, 86	0.242	0.117	2.066
	3	57-69	9, 47	0.154	0.117	1.311
	4	100-138	84, 83, 15, 24, 67, 8	0.154	0.117	1.311
	5	193-208	40, 30	0.111	0.117	0.947
	6	217-227	82, 14, 39	0.273	0.117	2.324
	7	247-268	81, 45, 80, 11	0.182	0.117	1.550
	8	278-297	79, 64, 23, 63, 78	0.250	0.117	2.131
	9	354-381	5, 59, 22, 77, 43, 76, 75	0.250	0.117	2.131
	10	385-405	74, 38, 58, 57	0.190	0.117	1.623
	11	440-450	73, 56, 55	0.273	0.117	2.324
	12	454-481	20, 72, 29, 1, 42, 28	0.214	0.117	1.826
	13	507-523	17, 71	0.118	0.117	1.003
	14	547-562	37, 36, 35	0.188	0.117	1.598
	15	568-591	27, 53, 34, 33	0.167	0.117	1.420
	16	603-614	13, 26	0.167	0.117	1.420
	17	631-650	70, 69, 52	0.150	0.117	1.278
	18	660-681	18, 7, 17, 51, 50	0.227	0.117	1.937
	19	700-719	41, 10, 4	0.150	0.117	1.278
	20	731-749	16, 49, 68, 3	0.211	0.117	1.794
NIH	1	3 to 12	25, 3	0.200	0.040	5.000
	2	20-43	15, 5, 4, 11, 10	0.208	0.040	5.208
	3*	415-435	18, 13	0.095	0.040	2.381
	4	663-676	1, 6	0.143	0.040	3.571
	5	700-715	30, 7, 3	0.188	0.040	4.688
	6	726-749	27, 9, 26, 24	0.167	0.040	4.167

*Nearby but not overlapping epitopes

Table 43
BIMAS-NIH/Parker algorithm Results for PSA

Rank	Start	Score
1	7	607
2	170	243
3	52	124
4	53	112
5	195	101
6	165	23
7	72	18
8	245	18
9	2	16
10	59	16
11	122	15
12	125	15
13	191	13
14	9	8
15	14	6
16	175	5
17	130	5

Table 44
SYFPEITHI (Rammensee algorithm) Results for PSA

Rank	Start	Score
1	72	26
2	170	22
3	53	22
4	7	22
5	234	21
6	166	21
7	140	21
8	66	21
9	241	20
10	175	20
11	12	20
12	41	19
13	20	19
14	14	19
15	130	18
16	124	18
17	121	18
18	47	18
19	17	18
20	218	17
21	133	17
22	125	17
23	122	17
24	118	17
25	110	17
26	67	17
27	52	17
28	21	17
29	16	17
30	2	17
31	184	16
32	179	16
33	158	16
34	79	16
35	73	16
36	4	16

Table 45

Prediction of clusters for prostate specific antigen (PSA)
Total AAs: 261
Total 9-mers: 253
SYFPEITHI 16: 36 9-mers
NIH 5: 17 9-mers

				Epitopes/AA		
	Cluster #	AAs	Epitopes (by rank)	Cluster	Whole Pr	Ratio
SYFPEITHI	1	2 to 29	30, 36, 4, 11, 14, 29, 19, 13, 28	0.321	0.138	2.330
	2	41-61	12, 18, 27, 3	0.190	0.138	1.381
	3	66-87	8, 26, 1, 35, 34	0.227	0.138	1.648
	4	110-148	25, 24, 17, 23, 16, 22, 15, 21, 7	0.184	0.138	1.332
	5	158-192	33, 6, 2, 10, 32, 31	0.171	0.138	1.243
	6	234-249	5, 9	0.125	0.138	0.906
	7*	118-133	24, 17, 23, 16, 22	0.313	0.138	2.266
	8*	118-138	24, 17, 23, 16, 22, 15	0.286	0.138	2.071
NIH	1	2-22	9, 1, 14, 15	0.190	0.065	2.924
	2	52-67	3, 4, 10	0.188	0.065	2.879
	3	122-138	11, 12, 17	0.176	0.065	2.709
	4	165-183	6, 2, 16	0.158	0.065	2.424
	5	191-203	13, 5	0.154	0.065	2.362
	6**	52-80	3, 4, 10, 7	0.138	0.065	2.118

*These clusters are internal to the less preferred cluster #4.

**Includes a nearby but not overlapping epitope.

Table 46
BIMAS-NIH/Parker algorithm Results for PSCA

Rank	Start	Score
1	43	153
2	5	84
3	7	79
4	109	36
5	105	25
6	108	24
7	14	21
8	20	18
9	115	17
10	42	15
11	36	15
12	99	9
13	58	8

Table 47
SYFPEITHI (Rammensee algorithm) Results for PSCA

Rank	Start	Score	Rank	Start	Score
1	108	30	17	54	19
2	14	30	18	12	19
3	105	29	19	4	19
4	5	28	20	1	19
5	115	26	21	112	18
6	99	26	22	101	18
7	7	26	23	98	18
8	109	24	24	51	18
9	53	23	25	43	18
10	107	21	26	106	17
11	20	21	27	104	17
12	8	21	28	83	17
13	13	20	29	63	17
14	102	19	30	50	17
15	60	19	31	3	17
16	57	19	32	9	16
			33	92	16

Table 48

Prediction of clusters for prostate stem cell antigen (PSCA)
Total AAs: 123
Total 9-mers: 115
SYFPEITHI 16: 33;
SYFPEITHI 20: 13
NIH 5: 13

					Epitopes/AA	
	Cluster #	AAs	Epitopes (by rank)	Cluster	Whole Pr.	Ratio
SYFPEITHI >16	1	1 to 28	20, 31, 19, 4, 7, 12, 33, 18, 13, 2, 11	0.393	0.268	1.464
	2	43-71	25, 30, 24, 9, 17, 16, 15, 29	0.276	0.268	1.028
	3	92-123	32, 23, 6, 27, 14, 22, 3, 26, 10, 1, 8, 21, 5	0.406	0.268	1.514
SYFPEITHI >20	1	5 to 28	4, 7, 12, 13, 2, 11	0.250	0.106	2.365
	2	99-123	6, 3, 10, 1, 8, 5	0.240	0.106	2.271
NIH	1	5 to 28	2, 3, 7, 8	0.167	0.106	1.577
	2	36-51	11, 10, 1	0.188	0.106	1.774
	3	99-123	12, 5, 6, 4, 9	0.200	0.106	1.892
	4*	105-116	5, 6, 4	0.250	0.106	2.365

*This cluster is internal to the less preferred cluster #3.

In tables 49-60 epitope prediction and cluster analysis data for each algorithm are presented together in a single table.

Table 49

Prediction of clusters for MAGE-1 (NIH algorithm)

Total AAs: 309
Total 9-mers: 301
NIH 5:19 9-mers

Cluster #	AAs	Epitope Rank	Start Position	NIH Score	Epitopes/AA Cluster	Whole Pr.	Ratio
1	18-32	16	18	9	0.133	0.063	2.112
		19	24	7			
2	101-113	14	101	11	0.154	0.063	2.442
		7	105	44			
3	146-159	9	146	32	0.143	0.063	2.263
		3	151	169			
4	169-202	10	169	32	0.176	0.063	2.796
		13	174	16			
		18	181	8			
		17	187	8			
		6	188	74			
		5	194	110			
5	264-277	2	264	190	0.143	0.063	2.263
		12	269	20			
6	278-290	1	278	743	0.154	0.063	2.437

11	282	28	

Table 50

Prediction of clusters for MAGE-1 (SYFPEITHI algorithm)

Total AAs: 309
Total 9-mers: 301
SYFPEITHI 16: 46 9-mers

Cluster #	Aas	Epitope Rank	Start Position	SYFPEITHI Score	Epitopes/AA Cluster	Whole	Ratio
1	7-49	22	7	19	0.233	0.153	1.522
		9	15	22			
		27	18	18			
		16	20	20			
		28	22	18			
		29	24	18			
		33	31	17			
		30	35	18			
		2	38	26			
		17	41	20			
2	89-132	10	89	22	0.273	0.153	1.783
		18	92	20			
		7	93	23			
		23	96	19			
		43	98	16			
		4	101	25			
		8	105	23			
		34	107	17			
		35	108	17			
		36	113	17			
		37	118	17			
		19	124	20			
3	167-203	44	167	16	0.270	0.153	1.766
		20	169	20			
		12	174	21			
		24	181	19			
		6	187	24			
		31	188	18			
		25	191	19			
		38	192	17			
		1	194	27			
		13	195	21			
4	230-246	14	230	21	0.118	0.153	0.769
		39	238	17			
5	264-297	15	264	21	0.235	0.153	1.538
		32	269	18			
		40	270	17			
		26	271	19			
		46	275	16			
		3	278	26			
		21	282	20			
		41	289	17			

Table 51

Prediction of clusters for MAGE-2 (NIH algorithm)

Total AAs: 314
Total 9-mers: 308
NIH >= 5: 20 9-mers

Cluster #	AAs	Epitope Rank	Start Position	NIH Score	Cluster	Epitope/AA Whole Pr.	Ratio
1	101-120	18	101	5.373	0.150	0.065	2.310
		16	108	6.756			
		1	112	2800.697			
2	153-167	8	153	31.883	0.200	0.065	3.080
		4	158	168.552			
		7	159	32.138			
3	169-211	14	169	8.535	0.209	0.065	3.223
		19	174	5.346			
		6	176	49.993			
		11	181	15.701			
		15	188	7.536			
		12	195	12.809			
		5	200	88.783			
		10	201	16.725			
		17	203	5.609			
4	271-284	3	271	398.324	0.143	0.065	2.200
		9	276	19.658			

Table 52

Prediction of clusters for MAGE-2 (SYFPEITHI algorithm)

Total AAs: 314
Total 9-mers: 308
SYFPEITHI 16: 52 9-mers

Cluster #	AAs	Epitope Rank	Start Position	SYFPEITHI Score	Cluster	Epitopes/AA Whole Pr.	Ratio
1	15-32	13	15	21	0.278	0.169	1.645
		29	18	18			
		43	20	16			
		30	22	18			
		21	24	19			
2	37-56	31	37	18	0.250	0.169	1.481
		16	40	20			
		44	44	16			
		14	45	21			
		22	48	19			
3	96-133	36	96	17	0.211	0.169	1.247
		46	101	16			
		6	108	25			
		47	109	16			
		2	112	27			
		37	120	17			
		38	125	17			
		17	131	20			
4	153-216	12	153	22	0.344	0.169	2.036
		39	158	17			
		7	159	25			
		23	161	19			
		24	162	19			
		48	164	16			
		49	167	16			
		32	170	18			
		50	171	16			
		4	174	26			
		9	176	24			
		51	177	16			
		15	181	21			
		25	188	19			
		18	194	20			
		33	195	18			
		19	198	20			
		3	200	27			
		1	201	28			
		40	202	17			
		10	203	23			
		52	208	16			
5	237-254	26	237	19	0.167	0.169	0.987
		27	245	19			
		34	246	18			
6	271-299	8	271	25	0.241	0.169	1.430
		35	276	18			
		41	277	17			
		11	278	23			
		28	283	19			
		20	285	20			
		42	291	17			

Table 53

Prediction of clusters for MAGE-3 (NIH algorithm)

Total AAs: 314
Total 9-mers: 308
NIH 5: 22 9-mers

Cluster #	AAs	Epitope Rank	Start Position	NIH Score	Epitopes/AA Cluster	Epitopes/AA Whole Pr.	Ratio
1	101-120	15	101	11.002	0.200	0.071	2.800
		21	105	6.488			
		8	108	49.134			
		2	112	339.313			
2	153-167	18	153	7.776	0.200	0.071	2.800
		6	158	51.77			
		22	159	5.599			
3	174-209	17	174	8.832	0.194	0.071	2.722
		7	176	49.993			
		13	181	15.701			
		19	188	7.536			
		14	195	12.809			
		5	200	88.783			
		12	201	16.725			
4	237-251	16	237	10.868	0.200	0.071	2.800
		4	238	148.896			
		20	243	6.88			
5	271-284	1	271	2655.495	0.143	0.071	2.000
		11	276	19.658			

Table 54

Prediction of clusters for MAGE-3 (SYFPEITHI algorithm)

Total AAs: 314
Total 9-mers: 308
SYFPEITHI 16: 47 9-mers

Cluster #	AAs	Epitope Rank	Start Position	SYFPEITHI Score	Cluster	Epitopes/AA Whole Pr.	Ratio
1	15-32	12	15	21	0.278	0.153	1.820
		26	18	18			
		37	20	16			
		27	22	18			
		18	24	19			
2	38-56	38	38	16	0.263	0.153	1.725
		15	40	20			
		39	44	16			
		13	45	21			
		19	48	19			
3	101-142	28	101	18	0.190	0.153	1.248
		40	105	16			
		1	108	31			
		6	112	25			
		31	120	17			
		32	125	17			
		16	131	20			
		41	134	16			
4	153-216	20	153	19	0.313	0.153	2.048
		29	156	18			
		33	158	17			
		21	159	19			
		34	161	17			
		42	164	16			
		43	167	16			
		10	174	22			
		8	176	23			
		14	181	21			
		22	188	19			
		44	193	16			
		11	194	22			
		23	195	19			
		45	197	16			
		17	198	20			
		3	200	27			
		2	201	28			
		35	202	17			
		46	208	16			
5	220-230	5	220	26	0.182	0.153	1.191
		47	222	16			
6	237-246	7	237	25	0.200	0.153	1.311
		9	238	23			
7	271-293	4	271	27	0.217	0.153	1.425
		30	276	18			
		24	278	19			
		36	283	17			
		25	285	19			

Table 55

Prediction of clusters for PRAME (NIH algorithm)

Total AAs: 509
Total 9-mers: 501
NIH 5: 40 9-mers

Cluster #	AAs	Epitope Rank	Start Position	NIH Score	Cluster	Epitopes/AA Whole Pr.	Ratio
1	33-47	20	33	18	0.133	0.080	1.670
		17	39	21			
2	71-81	9	71	50	0.2	0.07984	2.505
		32	73	7			
3	99-108	23	100	15	0.2	0.07984	2.505
		24	99	13			
4	126-135	38	126	5	0.2	0.07984	2.505
		35	127	6			
5	224-246	5	224	124	0.130	0.080	1.634
		8	230	63			
		39	238	5			
6	290-303	18	290	18	0.214	0.080	2.684
		14	292	23			
		7	295	66			
7	305-324	28	305	10	0.200	0.080	2.505
		30	308	8			
		25	312	13			
		36	316	6			
8	394-409	2	394	182	0.188	0.080	2.348
		12	397	42			
		31	401	7			
9	422-443	10	422	49	0.227	0.080	2.847
		3	425	182			
		34	431	7			
		29	432	9			
		4	435	160			
10	459-487	15	459	21	0.172	0.080	2.159
		11	462	45			
		22	466	15			
		40	472	5			
		37	479	6			

Table 56

Prediction of clusters for PRAME (SYFPEITHI algorithm)

Total AAs: 509
Total 9-mers: 501
SYFPEITHI 17: 80 9-mers

Cluster #	AAs	Epitope Rank	Start Position	SYFPEITHI Score	Epitopes/AA Cluster	Epitopes/AA Whole Pr.	Ratio
1	18-59	65	18	17	0.238	0.160	1.491
		50	21	18			
		66	26	17			
		35	33	20			
		22	34	22			
		51	37	18			
		5	39	27			
		23	40	22			
		13	44	24			
		46	51	19			
2	78-115	36	78	20	0.263	0.160	1.648
		67	80	17			
		52	84	18			
		24	86	22			
		53	91	18			
		25	93	22			
		9	99	25			
		8	100	26			
		54	103	18			
		55	107	18			
3	191-202	56	191	18	0.167	0.160	1.044
		38	194	20			
4	205-215	26	205	22	0.182	0.160	1.139
		27	207	22			
5	222-238	47	222	19	0.235	0.160	1.474
		14	224	24			
		69	227	17			
		57	230	18			
6	241-273	70	241	17	0.212	0.160	1.328
		15	248	24			
		71	255	17			
		30	258	21			
		39	259	20			
		58	261	18			
		40	265	20			
7.	290-342	72	290	17	0.208	0.160	1.300
		48	293	19			
		31	298	21			
		73	301	17			
		18	305	23			
		6	308	27			
		10	312	25			
		19	316	23			
		28	319	22			

Prediction of clusters for PRAME (SYFPEITHI algorithm)

Total AAs: 509
Total 9-mers: 501
SYFPEITHI 17: 80 9-mers

Cluster #	AAs	Epitope Rank	Start Position	SYFPEITHI Score	Epitopes/AA Cluster	Epitopes/AA Whole Pr.	Ratio
		41	326	20			
		74	334	17			
8	343-363	59	343	18	0.238	0.160	1.491
		60	348	18			
		75	351	17			
		20	353	23			
		76	355	17			
9	364-447	49	364	19	0.250	0.160	1.566
		32	371	21			
		11	372	25			
		61	375	18			
		77	382	17			
		21	390	23			
		78	391	17			
		1	394	30			
		42	397	20			
		62	403	18			
		33	410	21			
		43	418	20			
		34	419	21			
		7	422	27			
		2	425	29			
		79	426	17			
		63	428	18			
		64	431	18			
		12	432	25			
		16	435	24			
		80	439	17			
10	455-474	29	455	22	0.200	0.160	1.253
		17	459	24			
		4	462	28			
		3	466	29			

Table 57
Predication of clusters for CEA (NIH algorithm)

Total AAs:702
Total 9-mers: 694
NIH 5: 30 9-mers

Cluster #	AA	Peptides Rank	Start Position	Score	Cluster	Peptides/AAs Whole Pr.	Ratio
1	17-32	5	17	79.041	0.188	0.043	4.388
		7	18	46.873			
		20	24	12.668			
2	113-129	2	113	167.991	0.118	0.043	2.753
		15	121	21.362			
3	172-187	25	172	9.165	0.125	0.043	2.925
		14	179	27.995			
4	278-291	30	278	5.818	0.143	0.043	3.343
		17	283	19.301			
5	350-365	9	350	43.075	0.125	0.043	2.925
		12	357	27.995			
6	528-543	8	528	43.075	0.125	0.043	2.925
		13	535	27.995			
7	631-645	23	631	9.563	0.200	0.043	4.680
		19	634	13.381			
		24	637	9.245			
8	691-702	1	691	196.407	0.167	0.043	3.900
		27	694	7.769			

Table 58
Predication of clusters for CEA (SYFPEITHI algorithm)

Total AAs:702
Total 9-mers: 694
SYFPEITHI 16: 81 9-mers

Cluster #	AA	Peptides Rank	Start Position	Score	Peptides/AAs Cluster	Peptides/AAs Whole Pr.	Peptides/AAs Ratio
1	5-36	67	5	16	0.250	0.117	2.140
		23	12	19			
		24	16	19			
		9	17	22			
		25	18	19			
		32	19	18			
		68	23	16			
		33	28	18			
2	37-62	41	37	17	0.269	0.117	2.305
		20	44	20			
		26	45	19			
		42	46	17			
		27	50	19			
		43	53	17			
		44	54	17			
3	99-115	14	99	21	0.235	0.117	2.014
		5	100	23			
		45	104	17			
		34	107	18			
4	116-129	69	116	16	0.143	0.117	1.223
		21	121	20			
5	172-187	46	172	17	0.125	0.117	1.070
		70	179	16			
6	192-202	3	192	24	0.182	0.117	1.557
		47	194	17			
7	226-241	48	226	17	0.188	0.117	1.605
		49	229	17			
		15	233	21			
8	307-318	11	307	22	0.250	0.117	2.140
		71	308	16			
		51	310	17			
9	319-349	52	319	17	0.129	0.117	1.105
		53	327	17			
		72	335	16			
		35	341	18			
10	370-388	12	370	22	0.211	0.117	1.802
		54	372	17			
		74	375	16			
		6	380	23			
11	403-419	56	403	17	0.235	0.117	2.014
		57	404	17			

		58	407	17			
		28	411	19			
12	427-442	59	427	17	0.188	0.117	1.605
		75	432	16			
		76	434	16			
13	450-462	77	450	16	0.154	0.117	1.317
		13	454	22			
14	488-505	36	488	18	0.167	0.117	1.427
		18	492	21			
		60	497	17			
15	548-558	4	548	24	0.182	0.117	1.557
		61	550	17			
16	565-577	62	565	17	0.154	0.117	1.317
		19	569	21			
17	579-597	78	579	16	0.143	0.117	1.223
		79	582	16			
		7	589	23			
18	605-618	2	605	25	0.143	0.117	1.223
		38	610	18			
19	631-669	29	631	19	0.154	0.117	1.317
		63	637	17			
		80	644	16			
		64	652	17			
		39	660	18			
		81	661	16			
20	675-702	22	675	20	0.286	0.117	2.446
		30	683	19			
		31	687	19			
		40	688	18			
		65	690	17			
		1	691	31			
		66	692	17			
		8	694	23			

Table 59
Predication of clusters for SCP-1 (NIH algorithm)

Total AAs: 976
Total 9-mers: 968
NIH 5: 37 9-mers

Cluster #	AA	Peptides Rank	Start Position	Score	Cluster	Peptides/AAs Whole Pr.	Ratio
1	101-116	15	101	40.589	0.125	0.038	3.270
		13	108	57.255			
2*	281-305	14	281	44.944	0.12	0.038	3.139
		24	288	15.203			
		17	297	32.857			
3	431-447	8	431	80.217	0.073	0.038	1.914
		26	438	11.861			
		4	439	148.896			
4	557-579	11	557	64.335	0.174	0.038	4.550
		19	560	24.937			
		6	564	87.586			
		18	571	32.765			
5	635-650	10	635	69.552	0.125	0.038	3.270
		34	642	6.542			
6	755-767	36	755	5.599	0.154	0.038	4.025
		35	759	5.928			
7	838-854	2	838	284.517	0.118	0.038	3.078
		28	846	11.426			

Table 60
Predication of clusters for SCP-1

Total AAs: 976
Total 9-mers: 968
Rammensee 16: 118 9-mers

Cluster #	AA	Peptides Rank	Start Position	Score	Cluster	Peptides/AAs Whole Pr.	Ratio
1	8-28	99	8	16	0.143	0.121	1.182
		77	15	17			
		100	20	16			
2	63-80	78	63	17	0.222	0.121	1.838
		50	66	19			
		102	69	16			
		60	72	18			
3	94-123	79	94	17	0.133	0.121	1.103
		12	101	23			
		17	108	22			
		103	115	16			
4	126-158	35	126	20	0.182	0.121	1.504
		36	133	20			
		51	139	19			

		80	140	17			
		61	143	18			
		37	150	20			
5	161-189	38	161	20	0.207	0.121	1.711
		52	165	19			
		81	171	17			
		82	177	17			
		62	178	18			
		39	181	20			
6	213-230	40	213	20	0.167	0.121	1.379
		13	220	23			
		28	222	21			
7	235-250	63	235	18	0.125	0.121	1.034
		18	242	22			
8	260-296	83	260	17	0.243	0.121	2.012
		105	262	16			
		84	267	17			
		106	269	16			
		41	270	20			
		64	271	18			
		85	274	17			
		19	281	22			
		3	288	25			
9	312-338	108	312	16	0.148	0.121	1.225
		29	319	21			
		30	323	21			
		65	330	18			
10	339-355	66	339	18	0.235	0.121	1.946
		31	340	21			
		42	344	20			
		53	347	19			
11	376-447	54	376	19	0.194	0.121	1.608
		43	382	20			
		44	386	20			
		20	390	22			
		55	397	19			
		6	404	24			
		86	407	17			
		45	411	20			
		67	417	18			
		21	425	22			
		46	431	20			
		68	432	18			
		32	438	21			
		7	439	24			
12	455-488	33	455	21	0.235	0.121	1.946
		47	459	20			
		56	462	19			
		87	463	17			
		88	466	17			
		14	470	23			
		109	473	16			

		34	480	21			
13	515-530	57	515	19	0.125	0.121	1.034
		22	522	22			
14	557-590	8	557	24	0.147	0.121	1.216
		23	564	22			
		9	571	24			
		90	575	17			
		58	582	19			
15	610-625	69	610	18	0.125	0.121	1.034
		91	617	17			
16	633-668	92	633	17	0.222		
		10	635	24			
		70	638	18			
		93	640	17			
		48	642	20			
		49	645	20			
		111	652	16			
		112	660	16			
17	674-685	71	674	18	0.167	0.121	1.379
		11	677	24			
18	687-702	1	687	26	0.125	0.121	1.034
		94	694	17			
19	744-767	113	744	16	0.250	0.121	2.068
		95	745	17			
		4	745	25			
		24	752	22			
		2	755	26			
		72	759	18			
20	812-827	97	812	17	0.125	0.121	1.034
		115	819	16			
21	838-857	116	838	16	0.150	0.121	1.241
		25	846	22			
		74	849	18			
22	896-913	117	896	16	0.222	0.121	1.838
		98	899	17			
		26	902	22			
		76	905	18			

The embodiments of the invention are applicable to and contemplate variations in the sequences of the target antigens provided herein, including those disclosed in the various databases that are accessible by the world wide web. Specifically for the specific sequences disclosed herein, variation in sequences can be found by using the provided accession numbers to access information for each antigen.

TYROSINASE PROTEIN; SEQ ID NO 2

1 MLLAVLYCLL WSFQTSAGHF PRACVSSKNL MEKECCPPWS GDRSPCGQLS GRGSCQNILL
61 SNAPLGPQFP FTGVDDRESW PSVFYNRTCQ CSGNFMGFNC GNCKFGFWGP NCTERRLLVR
121 RNIFDLSAPE KDKFFAYLTL AKHTISSDYV IPIGTYGQMK NGSTPMFNDI NIYDLFVWMH
181 YYVSMDALLG GSEIWRDIDF AHEAPAFLPW HRLFLLRWEQ EIQKLTGDEN FTIPYWDWRD
241 AEKCDICTDE YMGGQHPTNP NLLSPASFFS SWQIVCSRLE EYNSHQSLCN GTPEGPLRRN
301 PGNHDKSRTP RLPSSADVEF CLSLTQYESG SMDKAANFSF RNTLEGFASP LTGIADASQS
361 SMHNALHIYM NGTMSQVQGS ANDPIFLLHH AFVDSIFEQW LRRHRPLQEV YPEANAPIGH
421 NRESYMVPFI PLYRNGDFFI SSKDLGYDYS YLQDSDPDSF QDYIKSYLEQ ASRIWSWLLG
481 AAMVGAVLTA LLAGLVSLLC RHKRKQLPEE KQPLLMEKED YHSLYQSHL

SSX-2 PROTEIN; SEQ ID NO 3

1 MNGDDAFARR PTVGAQIPEK IQKAFDDIAK YFSKEEWEKM KASEKIFYVY MKRKYEAMTK
61 LGFKATLPPF MCNKRAEDFQ GNDLDNDPNR GNQVERPQMT FGRLQGISPK IMPKKPAEEG
121 NDSEEVPEAS GPQNDGKELC PPGKPTTSEK IHERSGPKRG EHAWTHRLRE RKQLVIYEEI
181 SDPEEDDE

PSMA PROTEIN; SEQ ID NO 4

1 MWNLLHETDS AVATARRPRW LCAGALVLAG GFFLLGFLFG WFIKSSNEAT NITPKHNMKA
61 FLDELKAENI KKFLYNFTQI PHLAGTEQNF QLAKQIQSQW KEFGLDSVEL AHYDVLLSYP
121 NKTHPNYISI INEDGNEIFN TSLFEPPPPG YENVSDIVPP FSAFSPQGMP EGDLVYVNYA
181 RTEDFFKLER DMKINCSGKI VIARYGKVFR GNKVKNAQLA GAKGVILYSD PADYFAPGVK
241 SYPDGWNLPG GGVQRGNILN LNGAGDPLTP GYPANEYAYR RGIAEAVGLP SIPVHPIGYY
301 DAQKLLEKMG GSAPPDSSWR GSLKVPYNVG PGFTGNFSTQ KVKMHIHSTN EVTRIYNVIG
361 TLRGAVEPDR YVILGGHRDS WVFGGIDPQS GAAVVHEIVR SFGTLKKEGW RPRRTILFAS
421 WDAEEFGLLG STEWAEENSR LLQERGVAYI NADSSIEGNY TLRVDCTPLM YSLVHNLTKE
481 LKSPDEGFEG KSLYESWTKK SPSPEFSGMP RISKLGSGND FEVFFQRLGI ASGRARYTKN
541 WETNKFSGYP LYHSVYETYE LVEKFYDPMF KYHLTVAQVR GGMVFELANS IVLPFDCRDY

601 AVVLRKYADK IYSISMKHPQ EMKTYSVSFD SLFSAVKNFT EIASKFSERL QDFDKSNPIV
661 LRMMNDQLMF LERAFIDPLG LPDRPFYRHV IYAPSSHNKY AGESFPGIYD ALFDIESKVD
721 PSKAWGEVKR QIYVAAFTVQ AAAETLSEVA

Homo sapiens tyrosinase (oculocutaneous albinism IA) (TYR), mRNA.;
ACCESSION NM_000372
VERSION NM_000372.1 GI:4507752
SEQ ID NO 2
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CKFGFWGPNCTERRLLVRRNIFDLSAPEKDKFFAYLTLAKHTISSDYVIPIGTYGQMK

NGSTPMFNDINIYDLFVWMHYYVSMDALLGGSEIWRDIDFAHEAPAFLPWHRLFLLRW

EQEIQKLTGDENFTIPYWDWRDAEKCDICTDEYMGGQHPTNPNLLSPASFFSSWQIVC

SRLEEYNSHQSLCNGTPEGPLRRNPGNHDKSRTPRLPSSADVEFCLSLTQYESGSMDK

AANFSFRNTLEGFASPLTGIADASQSSMHNALHIYMNGTMSQVQGSANDPIFLLHHAF

VDSIFEQWLRRHRPLQEVYPEANAPIGHNRESYMVPFIPLYRNGDFFISSKDLGYDYS

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EEKQPLLMEKEDYHSLYQSHL"

SEQ ID NO 5
ORIGIN
1 atcactgtag tagtagctgg aaagagaaat ctgtgactcc aattagccag ttcctgcaga
61 ccttgtgagg actagaggaa gaatgctcct ggctgttttg tactgcctgc tgtggagttt
121 ccagacctcc gctggccatt tccctagagc ctgtgtctcc tctaagaacc tgatggagaa
181 ggaatgctgt ccaccgtgga gcggggacag gagtccctgt ggccagcttt caggcagagg
241 ttcctgtcag aatatccttc tgtccaatgc accacttggg cctcaatttc ccttcacagg
301 ggtggatgac cgggagtcgt ggccttccgt cttttataat aggacctgcc agtgctctgg
361 caacttcatg ggattcaact gtggaaactg caagtttggc ttttggggac caaactgcac
421 agagagacga ctcttggtga gaagaaacat cttcgatttg agtgccccag agaaggacaa
481 atttttgcc tacctcactt tagcaaagca taccatcagc tcagactatg tcatccccat

541 agggacctat ggccaaatga aaaatggatc aacacccatg tttaacgaca tcaatattta
601 tgacctcttt gtctggatgc attattatgt gtcaatggat gcactgcttg ggggatctga
661 aatctggaga gacattgatt ttgcccatga agcaccagct tttctgcctt ggcatagact
721 cttcttgttg cggtgggaac aagaaatcca gaagctgaca ggagatgaaa acttcactat
781 tccatattgg gactggcggg atgcagaaaa gtgtgacatt tgcacagatg agtacatggg
841 aggtcagcac cccacaaatc ctaacttact cagcccagca tcattcttct cctcttggca
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1081 taaagctgcc aatttcagct ttagaaatac actggaagga tttgctagtc cacttactgg
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1261 tgacagtatt tttgagcagt ggctccgaag gcaccgtcct cttcaagaag tttatccaga
1321 agccaatgca cccattggac ataaccggga atcctacatg gttccttta taccactgta
1381 cagaaatggt gatttcttta tttcatccaa agatctgggc tatgactata gctatctaca
1441 agattcagac ccagactctt ttcaagacta cattaagtcc tatttggaac aagcgagtcg
1501 gatctggtca tggctccttg gggcggcgat ggtaggggcc gtcctcactg ccctgctggc
1561 agggcttgtg agcttgctgt gtcgtcacaa gagaaagcag cttcctgaag aaaagcagcc
1621 actcctcatg gagaaagagg attaccacag cttgtatcag agccatttat aaaaggctta
1681 ggcaatagag tagggccaaa aagcctgacc tcactctaac tcaaagtaat gtccaggttc
1741 ccagagaata tctgctggta tttttctgta aagaccattt gcaaaattgt aacctaatac
1801 aaagtgtagc cttcttccaa ctcaggtaga acacacctgt ctttgtcttg ctgttttcac
1861 tcagcccttt taacattttc ccctaagccc atatgtctaa ggaaaggatg ctatttggta
1921 atgaggaact gttatttgta tgtgaattaa agtgctctta tttt

Homo sapiens synovial sarcoma, X breakpoint 2 (SSX2), mRNA.
ACCESSION NM_003147

VERSION NM_003147.1 GI:10337582
SEQ ID NO 3

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RLQGISPKIMPKKPAEEGNDSEEVPEASGPQNDGKELCPPGKPTTSEKIHERSGPKRG
EHAWTHRLRERKQLVIYEEISDPEEDDE"

SEQ ID NO 6
ORIGIN
1 ctctctttcg attcttccat actcagagta cgcacggtct gattttctct
ttggattctt
61 ccaaaatcag agtcagactg ctcccggtgc catgaacgga gacgacgcct
ttgcaaggag
121 acccacggtt ggtgctcaaa taccagagaa gatccaaaag gccttcgatg
atattgccaa
181 atacttctct aaggaagagt gggaaaagat gaaagcctcg gagaaaatct
tctatgtgta
241 tatgaagaga aagtatgagg ctatgactaa actaggtttc aaggccaccc
tcccaccttt
301 catgtgtaat aaacgggccg aagacttcca ggggaatgat ttggataatg
accctaaccg
361 tgggaatcag gttgaacgtc ctcagatgac tttcggcagg ctccagggaa
tctccccgaa
421 gatcatgccc aagaagccag cagaggaagg aaatgattcg gaggaagtgc
cagaagcatc
481 tggcccacaa aatgatggga aagagctgtg ccccccggga aaaccaacta
cctctgagaa
541 gattcacgag agatctggac ccaaaagggg ggaacatgcc tggacccaca
gactgcgtga
601 gagaaaacag ctggtgattt atgaagagat cagcgaccct gaggaagatg
acgagtaact
661 cccctcaggg atacgacaca tgcccatgat gagaagcaga acgtggtgac
ctttcacgaa
721 catgggcatg gctgcggacc cctcgtcatc aggtgcatag caagtg

Homo sapiens folate hydrolase (prostate-specific membrane antigen)
1 (FOLH1), mRNA.
ACCESSION NM_004476
VERSION NM_004476.1 GI:4758397

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SSNEATNITPKHNMKAFLDELKAENIKKFLYNFTQIPHLAGTEQNFQLAKQIQSQWKE

FGLDSVELAHYDVLLSYPNKTHPNYISIINEDGNEIFNTSLFEPPPPGYENVSDIVPP

FSAFSPQGMPEGDLVYVNYARTEDFFKLERDMKINCSGKIVIARYGKVFRGNKVKNAQ

LAGAKGVILYSDPADYFAPGVKSYPDGWNLPGGGVQRGNILNLNGAGDPLTPGYPANE

YAYRRGIAEAVGLPSIPVHPIGYYDAQKLLEKMGGSAPPDSSWRGSLKVPYNVGPGFT

GNFSTQKVKMHIHSTNEVTRIYNVIGTLRGAVEPDRYVILGGHRDSWVFGGIDPQSGA

AVVHEIVRSFGTLKKEGWRPRRTILFASWDAEEFGLLGSTEWAEENSRLLQERGVAYI

NADSSIEGNYTLRVDCTPLMYSLVHNLTKELKSPDEGFEGKSLYESWTKKSPSPEFSG

MPRISKLGSGNDFEVFFQRLGIASGRARYTKNWETNKFSGYPLYHSVYETYELVEKFY

DPMFKYHLTVAQVRGGMVFELANSIVLPFDCRDYAVVLRKYADKIYSISMKHPQEMKT

YSVSFDSLFSAVKNFTEIASKFSERLQDFDKSNPIVLRMMNDQLMFLERAFIDPLGLP

DRPFYRHVIYAPSSHNKYAGESFPGIYDALFDIESKVDPSKAWGEVKRQIYVAAFTVQ
AAAETLSEVA"

SEQ ID NO 7
ORIGIN

1 ctcaaaaggg gccggatttc cttctcctgg aggcagatgt tgcctctctc tctcgctcgg

61 attggttcag tgcactctag aaacactgct gtggtggaga aactggaccc caggtctgga

121 gcgaattcca gcctgcaggg ctgataagcg aggcattagt gagattgaga gagactttac

181 cccgccgtgg tggttggagg gcgcgcagta gagcagcagc acaggcgcgg gtcccgggag

241 gccggctctg ctcgcgccga gatgtggaat ctccttcacg aaaccgactc ggctgtggcc

301 accgcgcgcc gcccgcgctg gctgtgcgct ggggcgctgg tgctggcggg tggcttcttt

361 ctcctcggct tcctcttcgg gtggtttata aaatcctcca atgaagctac taacattact

421 ccaaagcata atatgaaagc atttttggat gaattgaaag ctgagaacat caagaagttc

481 ttatataatt ttacacagat accacattta gcaggaacag aacaaaactt tcagcttgca

541 aagcaaattc aatcccagtg gaaagaattt ggcctggatt ctgttgagct agcacattat

601 gatgtcctgt tgtcctaccc aaataagact catcccaact acatctcaat aattaatgaa

661 gatggaaatg agattttcaa cacatcatta tttgaaccac ctcctccagg atatgaaaat

721 gtttcggata ttgtaccacc tttcagtgct ttctctcctc aaggaatgcc agagggcgat

781 ctagtgtatg ttaactatgc acgaactgaa gacttcttta aattggaacg ggacatgaaa

841 atcaattgct ctgggaaaat tgtaattgcc agatatggga aagttttcag aggaaataag

901 gttaaaaatg cccagctggc aggggccaaa ggagtcattc tctactccga ccctgctgac
961 tactttgctc ctggggtgaa gtcctatcca gatggttgga atcttcctgg aggtggtgtc
1021 cagcgtggaa atatcctaaa tctgaatggt gcaggagacc ctctcacacc aggttaccca
1081 gcaaatgaat atgcttatag gcgtggaatt gcagaggctg ttggtcttcc aagtattcct
1141 gttcatccaa ttggatacta tgatgcacag aagctcctag aaaaaatggg tggctcagca
1201 ccaccagata gcagctggag aggaagtctc aaagtgccct acaatgttgg acctggcttt
1261 actggaaact tttctacaca aaaagtcaag atgcacatcc actctaccaa tgaagtgaca
1321 agaatttaca atgtgatagg tactctcaga ggagcagtgg aaccagacag atatgtcatt
1381 ctgggaggtc accgggactc atgggtgttt ggtggtattg accctcagag tggagcagct
1441 gttgttcatg aaattgtgag gagctttgga acactgaaaa aggaagggtg gagacctaga
1501 agaacaattt tgtttgcaag ctgggatgca gaagaatttg gtcttcttgg ttctactgag
1561 tgggcagagg agaattcaag actccttcaa gagcgtggcg tggcttatat taatgctgac
1621 tcatctatag aaggaaacta cactctgaga gttgattgta caccgctgat gtacagcttg
1681 gtacacaacc taacaaaaga gctgaaaagc cctgatgaag gctttgaagg caaatctctt
1741 tatgaaagtt ggactaaaaa aagtccttcc ccagagttca gtggcatgcc caggataagc
1801 aaattgggat ctggaaatga ttttgaggtg ttcttccaac gacttggaat tgcttcaggc
1861 agagcacggt atactaaaaa ttgggaaaca aacaaattca gcggctatcc actgtatcac
1921 agtgtctatg aaacatatga gttggtggaa aagttttatg atccaatgtt taaatatcac
1981 ctcactgtgg cccaggttcg aggagggatg gtgtttgagc tagccaattc catagtgctc
2041 ccttttgatt gtcgagatta tgctgtagtt ttaagaaagt atgctgacaa aatctacagt
2101 atttctatga aacatccaca ggaaatgaag acatacagtg tatcatttga ttcacttttt
2161 tctgcagtaa agaattttac agaaattgct tccaagttca gtgagagact ccaggacttt
2221 gacaaaagca acccaatagt attaagaatg atgaatgatc aactcatgtt tctggaaaga
2281 gcatttattg atccattagg gttaccagac aggccttttt ataggcatgt catctatgct
2341 ccaagcagcc acaacaagta tgcaggggag tcattcccag gaatttatga tgctctgttt
2401 gatattgaaa gcaaagtgga cccttccaag gcctggggag aagtgaagag acagatttat

2461 gttgcagcct tcacagtgca ggcagctgca gagactttga gtgaagtagc ctaagaggat
2521 tctttagaga atccgtattg aatttgtgtg gtatgtcact cagaaagaat cgtaatgggt
2581 atattgataa attttaaaat tggtatattt gaaataaagt tgaatattat atataaaaaa
2641 aaaaaaaaaa aaa

Human melanocyte-specific (pmel 17) gene, exons 2-5, and complete cds.
ACCESSION U20093
VERSION U20093.1 GI:1142634
SEQ ID NO 70

/translation="MDLVLKRCLLHLAVIGALLAVGATKVPRNQDWLGVSRQLRTKAWNRQLYPEW
TEAQRLDCWRGGQVSLKVSNDGPTLIGANASFSIALNFPGSQKVLPDGQVIWVNNTIINGSQVWGG
QPVYPQETDDACIFPDGGPCPSGSWSQKRSFVYVWKTWGQYWQVLGGPVSGLSIGTGRAMLGTHTM
EVTVYHRRGSRSYVPLAHSSSAFTITDQVPFSVSVSQLRALDGGNKHFLRNQPLTFALQLHDPSGY
LAEADLSYTWDFGDSSGTLISRAPVVTHTYLEPGPVTAQVVLQAAIPLTSCGSSPVPGTTDGHRPT
AEAPNTTAGQVPTTEVVGTTPGQAPTAEPSGTTSVQVPTTEVISTAPVQMPTAESTGMTPEKVPVS
EVMGTTLAEMSTPEATGMTPAEVSIVVLSGTTAAQVTTTEWVETTARELPIPEPEGPDASSIMSTE
SITGSLGPLLDGTATLRLVKRQVPLDCVLYRYGSFSVTLDIVQGIESAEILQAVPSGEGDAFELTV
SCQGGLPKEACMEISSPGCQPPAQRLCQPVLPSPACQLVLHQILKGGSGTYCLNVSLADTNSLAVV
STQLIMPGQEAGLGQVPLIVGILLVLMAVVLASLIYRRRLMKQDFSVPQLPHSSSHWLRLPRIFCS
CPIGENSPLLSGQQV"

SEQ ID NO 80
ORIGIN
1 gtgctaaaaa gatgccttct tcatttggct gtgataggtg ctttgtggct gtgggggcta
61 caaaagtacc cagaaaccag gactggcttg gtgtctcaag gcaactcaga accaaagcct
121 ggaacaggca gctgtatcca gagtggacag aagcccagag acttgactgc tggagaggtg
181 gtcaagtgtc cctcaaggtc agtaatgatg ggcctacact gattggtgca aatgcctcct
241 tctctattgc cttgaacttc cctggaagcc aaaaggtatt gccagatggg caggttatct
301 gggtcaacaa taccatcatc aatgggagcc aggtgtgggg aggacagcca gtgtatcccc
361 aggaaactga cgatgcctgc atcttccctg atggtggacc ttgcccatct ggctcttggt
421 ctcagaagag aagctttgtt tatgtctgga agacctgggg tgagggactc ccttctcagc
481 ctatcatcca cacttgtgtt tacttctttc tacctgatca cctttctttt ggccgccccc
541 tccaccttaa cttctgtgat tttctctaat cttcattttc ctcttagatc ttttctcttt
601 cttagcacct agccccctc aagctctatc ataattcttt ctggcaactc ttggcctcaa

661 ttgtagtcct accccatgga atgcctcatt aggacccctt ccctgtcccc ccatatcaca
721 gccttccaaa caccctcaga agtaatcata cttcctgacc tcccatctcc agtgccgttt
781 cgaagcctgt ccctcagtcc cctttgacca gtaatctctt cttccttgct tttcattcca
841 aaaatgcttc aggccaatac tggcaagttc taggggccc agtgtctggg ctgagcattg
901 ggacaggcag ggcaatgctg ggcacacaca ccatggaagt gactgtctac catcgccggg
961 gatcccggag ctatgtgcct cttgctcatt ccagctcagc cttcaccatt actggtaagg
1021 gttcaggaag ggcaaggcca gttgtagggc aaagagaagg cagggaggct tggatggact
1081 gcaaaggaga aaggtgaaat gctgtgcaaa cttaaagtag aagggccagg aagacctagg
1141 cagagaaatg tgaggcttag tgccagtgaa gggccagcca gtcagcttgg agttggaggg
1201 tgtggctgtg aaaggagaag ctgtggctca ggcctggttc tcacctttc tggctccaat
1261 cccagaccag gtgcctttct ccgtgagcgt gtcccagttg cgggccttgg atggagggaa
1321 caagcacttc ctgagaaatc agcctctgac ctttgccctc cagctccatg accccagtgg
1381 ctatctggct gaagctgacc tctcctacac ctgggacttt ggagacagta gtggaaccct
1441 gatctctcgg gcacctgtgg tcactcatac ttacctggag cctggcccag tcactgccca
1501 ggtggtcctg caggctgcca ttcctctcac ctcctgtggc tcctccccag ttccaggcac
1561 cacagatggg cacaggccaa ctgcagaggc ccctaacacc acagctggcc aagtgcctac
1621 tacagaagtt gtgggtacta cacctggtca ggcgccaact gcagagccct ctggaaccac
1681 atctgtgcag gtgccaacca ctgaagtcat aagcactgca cctgtgcaga tgccaactgc
1741 agagagcaca ggtatgacac ctgagaaggt gccagtttca gaggtcatgg gtaccacact
1801 ggcagagatg tcaactccag aggctacagg tatgacacct gcagaggtat caattgtggt
1861 gctttctgga accacagctg cacaggtaac aactacagag tgggtggaga ccacagctag
1921 agagctacct atccctgagc ctgaaggtcc agatgccagc tcaatcatgt ctacggaaag
1981 tattacaggt tccctgggcc ccctgctgga tggtacagcc accttaaggc tggtgaagag
2041 acaagtcccc ctggattgtg ttctgtatcg atatggttcc ttttccgtca ccctggacat
2101 tgtccagggt attgaaagtg ccgagatcct gcaggctgtg ccgtccggtg aggggatgc
2161 atttgagctg actgtgtcct gccaaggcgg gctgcccaag gaagcctgca tggagatctc

2221 atcgccaggg tgccagcccc ctgcccagcg gctgtgccag cctgtgctac ccagcccagc
2281 ctgccagctg gttctgcacc agatactgaa gggtggctcg gggacatact gcctcaatgt
2341 gtctctggct gataccaaca gcctggcagt ggtcagcacc cagcttatca tgcctggtag
2401 gtccttggac agagactaag tgaggaggga agtggataga ggggacagct ggcaagcagc
2461 agacatgagt gaagcagtgc ctgggattct tctcacaggt caagaagcag gccttgggca
2521 ggttccgctg atcgtgggca tcttgctggt gttgatggct gtggtccttg catctctgat
2581 atataggcgc agacttatga agcaagactt ctccgtaccc cagttgccac atagcagcag
2641 tcactggctg cgtctacccc gcatcttctg ctcttgtccc attggtgaga atagcccccc
2701 cctcagtggg cagcaggtct gagtactctc atatgatgct gtgattttcc tggagttgac
2761 agaaacacct atatttcccc cagtcttccc tgggagacta ctattaactg aaataaa
//

Homo sapiens kallikrein 3, (prostate specific antigen) (KLK3), mRNA.
ACCESSION NM_001648
VERSION NM_001648.1 GI:4502172
SEQ ID NO 78

/translation="MWVPVVFLTLSVTWIGAAPLILSRIVGGWECEKHSQPWQVLVAS
RGRAVCGGVLVHPQWVLTAAHCIRNKSVILLGRHSLFHPEDTGQVFQVSHSFPHPLYDMSLLKNRF
LRPGDDSSHDLMLLRLSEPAELTDAVKVMDLPTQEPALGTTCYASGWGSIEPEEFLTPKKLQCVDL
HVISNDVCAQVHPQKVTKFMLCAGRWTGGKSTCSGDSGGPLVCNGVLQGITSWGSEPCALPERPSL
YTKVVHYRKWIKDTIVANP"

SEQ ID NO 86
ORIGIN
1 agccccaagc ttaccacctg cacccggaga gctgtgtgtc accatgtggg tcccggttgt
61 cttcctcacc ctgtccgtga cgtggattgg tgctgcaccc ctcatcctgt ctcggattgt
121 gggaggctgg gagtgcgaga agcattccca accctggcag gtgcttgtgg cctctcgtgg
181 cagggcagtc tgcggcggtg ttctggtgca cccccagtgg gtcctcacag ctgcccactg
241 catcaggaac aaaagcgtga tcttgctggg tcggcacagc ctgtttcatc ctgaagacac
301 aggccaggta tttcaggtca gccacagctt cccacacccg ctctacgata tgagcctcct
361 gaagaatcga ttcctcaggc caggtgatga ctccagccac gacctcatgc tgctccgcct

421 gtcagagcct gccgagctca cggatgctgt gaaggtcatg gacctgccca cccaggagcc
481 agcactgggg accacctgct acgcctcagg ctggggcagc attgaaccag aggagttctt
541 gaccccaaag aaacttcagt gtgtggacct ccatgttatt tccaatgacg tgtgtgcgca
601 agttcaccct cagaaggtga ccaagttcat gctgtgtgct ggacgctgga caggggggcaa
661 aagcacctgc tcgggtgatt ctgggggccc acttgtctgt aatggtgtgc ttcaaggtat
721 cacgtcatgg ggcagtgaac catgtgccct gcccgaaagg ccttccctgt acaccaaggt
781 ggtgcattac cggaagtgga tcaaggacac catcgtggcc aacccctgag caccctatc
841 aacccccctat tgtagtaaac ttggaacctt ggaaatgacc aggccaagac tcaagcctcc
901 ccagttctac tgacctttgt ccttaggtgt gaggtccagg gttgctagga aaagaaatca
961 gcagacacag gtgtagacca gagtgtttct taaatggtgt aattttgtcc tctctgtgtc
1021 ctggggaata ctggccatgc ctggagacat atcactcaat ttctctgagg acacagatag
1081 gatggggtgt ctgtgttatt tgtggggtac agagatgaaa gaggggtggg atccacactg
1141 agagagtgga gagtgacatg tgctggacac tgtccatgaa gcactgagca gaagctggag
1201 gcacaacgca ccagacactc acagcaagga tggagctgaa aacataaccc actctgtcct
1261 ggaggcactg ggaagcctag agaaggctgt gagccaagga gggagggtct tcctttggca
1321 tgggatgggg atgaagtaag gagagggact ggacccctg gaagctgatt cactatgggg
1381 ggaggtgtat tgaagtcctc cagacaaccc tcagatttga tgatttccta gtagaactca
1441 cagaaataaa gagctgttat actgtg
//

Human autoimmunogenic cancer/testis antigen NY-ESO-1 mRNA, complete cds.
ACCESSION U87459
VERSION U87459.1 GI:1890098
SEQ ID NO 74

/translation="MQAEGRGTGGSTGDADGPGGPGIPDGPGGNAGGPGEAG
ATGGRGPRGAGAARASGPGGGAPRGPHGGAASGLNGCCRCGARGPESRLLEF
YLAMPFATPMEAELARRSLAQDAPPLPVPGVLLKEFTVSGNILTIRLTAADH
RQLQLSISSCLQQLSLLMWITQCFLPVFLAQPPSGQRR"

SEQ ID NO 84
ORIGIN

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        1 atcctcgtgg gccctgacct tctctctgag agccgggcag aggctccgga
gccatgcagg
       61 ccgaaggccg gggcacaggg ggttcgacgg gcgatgctga tggcccagga
ggccctggca
      121 ttcctgatgg cccaggggge aatgctggcg gcccaggaga ggcgggtgcc
acgggcggca
      181 gaggtccccg gggcgcaggg gcagcaaggg cctcggggcc gggaggaggc
gccccgcggg
      241 gtccgcatgg cggcgcggct tcagggctga atggatgctg cagatgcggg
gccaggggge
      301 cggagagccg cctgcttgag ttctacctcg ccatgccttt cgcgacaccc
atggaagcag
      361 agctggcccg caggagcctg gcccaggatg ccccaccgct tcccgtgcca
ggggtgcttc
      421 tgaaggagtt cactgtgtcc ggcaacatac tgactatccg actgactgct
gcagaccacc
      481 gccaactgca gctctccatc agctcctgtc tccagcagct ttccctgttg
atgtggatca
      541 cgcagtgctt tctgcccgtg tttttggctc agcctccctc agggcagagg
cgctaagccc
      601 agcctggcgc cccttcctag gtcatgcctc ctcccctagg gaatggtccc
agcacgagtg
      661 gccagttcat tgtgggggcc tgattgtttg tcgctggagg aggacggctt
acatgtttgt
      721 ttctgtagaa aataaaactg agctacgaaa aa
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LAGE-1a protein [Homo sapiens].
ACCESSION   CAA11116
PID             g3255959
VERSION         CAA11116.1  GI:3255959

SEQ ID NO 75
ORIGIN
        1 mqaegrgtgg stgdadgpgg pgipdgpggn aggpgeagat ggrgprgaga
arasgprgga
       61 prgphggaas aqdgrcpcga rrpdsrllel hitmpfsspm eaelvrrils
rdaaplprpg
      121 avlkdftvsg nllfirltaa dhrqlqlsis sclqqlsllm witqcflpvf
laqapsgqrr
      181
//


LAGE-1b protein [Homo sapiens].
ACCESSION  CAA11117
PID             g3255960
VERSION         CAA11117.1  GI:3255960

SEQ ID NO 76
ORIGIN
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1 mqaegrgtgg stgdadgpgg pgipdgpggn aggpgeagat ggrgprgaga arasgprgga
61 prgphggaas aqdgrcpcga rrpdsrllel hitmpfsspm eaelvrrils rdaaplprpg
121 avlkdftvsg nllfmsvwdq dregagrmrv vgwglgsasp egqkardlrt pkhkvseqrp
181 gtpgpppeg aqgdgcrgva fnvmfsaphi
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Human antigen (MAGE-1) gene, complete cds.
ACCESSION M77481
VERSION M77481.1 GI:416114
SEQ ID NO 71

/translation="MSLEQRSLHCKPEEALEAQQEALGLVCVQAATSSSSPL
VLGTLEEVPTAGSTDPPQSPQGASAFPTTINFTRQRQPSEGSSSREEEGPST
SCILESLFRAVITKKVADLVGFLLLKYRAREPVTKAEMLESVIKNYKHCFPE
IFGKASESLQLVFGIDVKEADPTGHSYVLVTCLGLSYDGLLGDNQIMPKTGF
LIIVLVMIAMEGGHAPEEEIWEELSVMEVYDGREHSAYGEPRKLLTQDLVQE
KYLEYRQVPDSDPARYEFLWGPRALAETSYVKVLEYVIKVSARVRFFFPSLR
EAALREEEEGV"

SEQ ID NO 81
ORIGIN
1 ggatccaggc cctgccagga aaaatataag ggccctgcgt gagaacagag ggggtcatcc
61 actgcatgag agtggggatg tcacagagtc cagcccaccc tcctggtagc actgagaagc
121 cagggctgtg cttgcggtct gcaccctgag ggcccgtgga ttcctcttcc tggagctcca
181 ggaaccaggc agtgaggcct tggtctgaga cagtatcctc aggtcacaga gcagaggatg
241 cacagggtgt gccagcagtg aatgtttgcc ctgaatgcac accaagggcc ccacctgcca
301 caggacacat aggactccac agagtctggc ctcacctccc tactgtcagt cctgtagaat
361 cgacctctgc tggccggctg taccctgagt accctctcac ttcctccttc aggttttcag
421 gggacaggcc aacccagagg acaggattcc ctggaggcca cagaggagca ccaaggagaa
481 gatctgtaag taggcctttg ttagagtctc caaggttcag ttctcagctg aggcctctca
541 cacactccct ctctccccag gcctgtgggt cttcattgcc cagctcctgc ccacactcct
601 gcctgctgcc ctgacgagag tcatcatgtc tcttgagcag aggagtctgc actgcaagcc
661 tgaggaagcc cttgaggccc aacaagaggc cctgggcctg gtgtgtgtgc aggctgccac
721 ctcctcctcc tctcctctgg tcctgggcac cctggaggag gtgcccactg ctgggtcaac

781 agatcctccc cagagtcctc agggagcctc cgcctttccc actaccatca acttcactcg
841 acagaggcaa cccagtgagg gttccagcag ccgtgaagag gaggggccaa gcacctcttg
901 tatcctggag tccttgttcc gagcagtaat cactaagaag gtggctgatt tggttggttt
961 tctgctcctc aaatatcgag ccagggagcc agtcacaaag gcagaaatgc tggagagtgt
1021 catcaaaaat tacaagcact gttttcctga gatcttcggc aaagcctctg agtccttgca
1081 gctggtcttt ggcattgacg tgaaggaagc agaccccacc ggccactcct atgtccttgt
1141 cacctgccta ggtctctcct atgatggcct gctgggtgat aatcagatca tgcccaagac
1201 aggcttcctg ataattgtcc tggtcatgat tgcaatggag ggcggccatg ctcctgagga
1261 ggaaatctgg gaggagctga gtgtgatgga ggtgtatgat gggagggagc acagtgccta
1321 tggggagccc aggaagctgc tcacccaaga tttggtgcag gaaaagtacc tggagtaccg
1381 gcaggtgccg gacagtgatc ccgcacgcta tgagttcctg tggggtccaa gggccctcgc
1441 tgaaaccagc tatgtgaaag tccttgagta tgtgatcaag gtcagtgcaa gagttcgctt
1501 tttcttccca tccctgcgtg aagcagcttt gagagaggag gaagagggag tctgagcatg
1561 agttgcagcc aaggccagtg ggagggggac tgggccagtg caccttccag ggccgcgtcc
1621 agcagcttcc cctgcctcgt gtgacatgag gcccattctt cactctgaag agagcggtca
1681 gtgttctcag tagtaggttt ctgttctatt gggtgacttg gagatttatc tttgttctct
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1801 ttatgaatga cagcagtcac acagttctgt gtatatagtt taagggtaag agtcttgtgt
1861 tttattcaga ttgggaaatc cattctattt tgtgaattgg gataataaca gcagtggaat
1921 aagtacttag aaatgtgaaa aatgagcagt aaaatagatg agataaagaa ctaaagaaat
1981 taagagatag tcaattcttg ccttatacct cagtctattc tgtaaaattt ttaaagatat
2041 atgcatacct ggatttcctt ggcttctttg agaatgtaag agaaattaaa tctgaataaa
2101 gaattcttcc tgttcactgg ctcttttctt ctccatgcac tgagcatctg cttttggaa
2161 ggccctgggt tagtagtgga gatgctaagg taagccagac tcatacccac ccatagggtc
2221 gtagagtcta ggagctgcag tcacgtaatc gaggtggcaa gatgtcctct aaagatgtag
2281 ggaaaagtga gagaggggtg agggtgtggg gctccgggtg agagtggtgg agtgtcaatg

2341 ccctgagctg gggcattttg ggctttggga aactgcagtt ccttctgggg gagctgattg
2401 taatgatctt gggtggatcc
//

Human MAGE-2 gene exons 1-4, complete cds.
ACCESSION L18920
VERSION L18920.1 GI:436180
SEQ ID NO 72

/translation="MPLEQRSQHCKPEEGLEARGEALGLVGAQAPATEEQQTASSSSTLVEVT
LGEVPAADSPSPPHSPQGASSFSTTINYTLWRQSDEGSSNQEEEGPRMFPDLE
SEFQAAISRKMVELVHFLLLKYRAREPVTKAEMLESVLRNCQDFFPVIFSKASEYLQLVFGIE
VVEVVPISHLYILVTCLGLSYDGLLGDNQVMPKTGLLIIVLAIIAIEGDCAPEEKIWEELSML
EVFEGREDSVFAHPRKLLMQDLVQENYLEYRQVPGSDPACYEFLWGPRALIETSYVKVLHHTL
KIGGEPHISYPPLHERALREGEE"

SEQ ID NO 82
ORIGIN
1 attccttcat caaacagcca ggagtgagga agaggaccct cctgagtgag gactgaggat
61 ccacccctcac cacatagtgg gaccacagaa tccagctcag cccctcttgt cagccctggt
121 acacactggc aatgatctca ccccgagcac acccctcccc ccaatgccac ttcgggccga
181 ctcagagtca gagacttggt ctgaggggag cagacacaat cggcagagga tggcggtcca
241 ggctcagtct ggcatccaag tcaggacctt gagggatgac caaaggcccc tcccaccccc
301 aactcccccg accccaccag gatctacagc ctcaggatcc ccgtcccaat ccctaccct
361 acaccaacac catcttcatg cttaccccca ccccccatc cagatcccca tccgggcaga
421 atccggttcc acccttgccg tgaacccagg gaagtcacgg gcccggatgt gacgccactg
481 acttgcacat tggaggtcag aggacagcga gattctcgcc ctgagcaacg gcctgacgtc
541 ggcggaggga agcaggcgca ggctccgtga ggaggcaagg taagacgccg agggaggact
601 gaggcgggcc tcaccccaga cagagggccc ccaataatcc agcgctgcct ctgctgccgg
661 gcctggacca ccctgcaggg gaagacttct caggctcagt cgccaccacc tcaccccgcc
721 acccccgcc gctttaaccg cagggaactc tggcgtaaga gctttgtgtg accagggcag
781 ggctggttag aagtgctcag ggcccagact cagccaggaa tcaaggtcag gaccccaaga
841 ggggactgag ggcaacccac cccctaccct cactaccaat cccatccccc aacaccaacc
901 ccacccccat ccctcaaaca ccaaccccac ccccaaaccc cattcccatc tcctccccca

961 ccaccatcct ggcagaatcc ggctttgccc ctgcaatcaa cccacggaag ctccgggaat
1021 ggcggccaag cacgcggatc ctgacgttca catgtacggc taagggaggg aaggggttgg
1081 gtctcgtgag tatggccttt gggatgcaga ggaagggccc aggcctcctg gaagacagtg
1141 gagtccttag gggacccagc atgccaggac aggggcccca ctgtaccct gtctcaaact
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1261 ttggggccca gcctgcgagg agtcaagggg aggaagaaga gggaggactg aggggacctt
1321 ggagtccaga tcagtggcaa ccttgggctg ggggatcctg ggcacagtgg ccgaatgtgc
1381 cccgtgctca ttgcaccttc agggtgacag agagttgagg gctgtggtct gagggctggg
1441 acttcaggtc agcagaggga ggaatcccag gatctgccgg acccaaggtg tgccccctc
1501 atgaggactg gggatacccc cggcccagaa agaagggatg ccacagagtc tggaagtccc
1561 ttgttcttag ctctgggggga acctgatcag ggatggccct aagtgacaat ctcatttgta
1621 ccacaggcag gaggttgggg aaccctcagg gagataaggt gttggtgtaa agaggagctg
1681 tctgctcatt tcaggggtt gggggttgag aaagggcagt ccctggcagg agtaaagatg
1741 agtaacccac aggaggccat cataacgttc accctagaac caaaggggtc agccctggac
1801 aacgcacgtg ggggtaacag gatgtggccc ctcctcactt gtctttccag atctcaggga
1861 gttgatgacc ttgttttcag aaggtgactc aggtcaacac aggggcccca tctggtcgac
1921 agatgcagtg gttctaggat ctgccaagca tccaggtgga gagcctgagg taggattgag
1981 ggtacccctg ggccagaatg cagcaagggg gccccataga aatctgccct gcccctgcgg
2041 ttacttcaga gaccctgggc agggctgtca gctgaagtcc ctccattatc ctgggatctt
2101 tgatgtcagg gaaggggagg ccttggtctg aaggggctgg agtcaggtca gtagagggag
2161 ggtctcaggc cctgccagga gtggacgtga ggaccaagcg gactcgtcac ccaggacacc
2221 tggactccaa tgaatttgga catctctcgt tgtccttcgc gggaggacct ggtcacgtat
2281 ggccagatgt gggtcccctc atatccttct gtaccatatc agggatgtga gttcttgaca
2341 tgagagattc tcaagccagc aaaagggtgg gattaggccc tacaaggaga aaggtgaggg
2401 ccctgagtga gcacagaggg gaccctccac ccaagtagag tggggacctc acggagtctg
2461 gccaaccctg ctgagacttc tgggaatccg tggctgtgct tgcagtctgc acactgaagg

2521 cccgtgcatt cctctcccag gaatcaggag ctccaggaac caggcagtga ggccttggtc
2581 tgagtcagtg tcctcaggtc acagagcaga ggggacgcag acagtgccaa cactgaaggt
2641 ttgcctggaa tgcacaccaa gggccccacc cgcccagaac aaatgggact ccagagggcc
2701 tggcctcacc ctccctattc tcagtcctgc agcctgagca tgtgctggcc ggctgtaccc
2761 tgaggtgccc tcccacttcc tccttcaggt tctgaggggg acaggctgac aagtaggacc
2821 cgaggcactg gaggagcatt gaaggagaag atctgtaagt aagcctttgt cagagcctcc
2881 aaggttcagt tcagttctca cctaaggcct cacacacgct ccttctctcc ccaggcctgt
2941 gggtcttcat tgcccagctc ctgcccgcac tcctgcctgc tgccctgacc agagtcatca
3001 tgcctcttga gcagaggagt cagcactgca agcctgaaga aggccttgag gcccgaggag
3061 aggccctggg cctggtgggt gcgcaggctc ctgctactga ggagcagcag accgcttctt
3121 cctcttctac tctagtggaa gttaccctgg gggaggtgcc tgctgccgac tcaccgagtc
3181 ctccccacag tcctcaggga gcctccagct tctcgactac catcaactac actctttgga
3241 gacaatccga tgagggctcc agcaaccaag aagaggaggg gccaagaatg tttcccgacc
3301 tggagtccga gttccaagca gcaatcagta ggaagatggt tgagttggtt cattttctgc
3361 tcctcaagta tcgagccagg gagccggtca caaaggcaga aatgctggag agtgtcctca
3421 gaaattgcca ggacttcttt cccgtgatct tcagcaaagc ctccgagtac ttgcagctgg
3481 tctttggcat cgaggtggtg gaagtggtcc ccatcagcca cttgtacatc cttgtcacct
3541 gcctgggcct ctcctacgat ggcctgctgg gcgacaatca ggtcatgccc aagacaggcc
3601 tcctgataat cgtcctggcc ataatcgcaa tagagggcga ctgtgccctt gaggagaaaa
3661 tctgggagga gctgagtatg ttggaggtgt ttgaggggag ggaggacagt gtcttcgcac
3721 atcccaggaa gctgctcatg caagatctgg tgcaggaaaa ctacctggag taccggcagg
3781 tgcccggcag tgatcctgca tgctacgagt tcctgtgggg tccaagggcc ctcattgaaa
3841 ccagctatgt gaaagtcctg caccatacac taaagatcgg tggagaacct cacatttcct
3901 acccacccct gcatgaacgg gctttgagag agggagaaga gtgagtctca gcacatgttg
3961 cagccagggc cagtgggagg gggtctgggc cagtgcacct tccagggccc catccattag
4021 cttccactgc ctcgtgtgat atgaggccca ttcctgcctc tttgaagaga gcagtcagca

4081 ttcttagcag tgagtttctg ttctgttgga tgactttgag atttatcttt ctttcctgtt
4141 ggaattgttc aaatgttcct tttaacaaat ggttggatga acttcagcat ccaagtttat
4201 gaatgacagt agtcacacat agtgctgttt atatagttta ggggtaagag tcctgttttt
4261 tattcagatt gggaaatcca ttccattttg tgagttgtca cataataaca gcagtggaat
4321 atgtatttgc ctatattgtg aacgaattag cagtaaaata catgatacaa ggaactcaaa
4381 agatagttaa ttcttgcctt atacctcagt ctattatgta aaattaaaaa tatgtgtatg
4441 tttttgcttc tttgagaatg caaaagaaat taaatctgaa taaattcttc ctgttcactg
4501 gctcatttct ttaccattca ctcagcatct gctctgtgga aggccctggt agtagtgggg
//

Human MAGE-3 antigen (MAGE-3) gene, complete cds.
ACCESSION U03735
VERSION U03735.1 GI:468825
SEQ ID NO 73

/translation="MPLEQRSQHCKPEEGLEARGEALGLVGAQAPATEEQEAASSSSTLVEVTLGE
VPAAESPDPPQSPQGASSLPTTMNYPLWSQSYEDSSNQEEEGPSTFPDLESEFQAALSRKVAELVH
FLLLKYRAREPVTKAEMLGSVVGNWQYFFPVIFSKASSSLQLVFGIELMEVDPIGHLYIFATCLGL
SYDGLLGDNQIMPKAGLLIIVLAIIAREGDCAPEEKIWEELSVLEVFEGREDSILGDPKKLLTQHF
VQENYLEYRQVPGSDPACYEFLWGPRALVETSYVKVLHHMVKISGGPHISYPPLHEWVLREGEE"

SEQ ID NO 83
ORIGIN
1 acgcaggcag tgatgtcacc cagaccacac cccttccccc aatgccactt caggggggtac
61 tcagagtcag agacttggtc tgaggggagc agaagcaatc tgcagaggat ggcggtccag
121 gctcagccag gcatcaactt caggaccctg agggatgacc gaaggccccg cccacccacc
181 cccaactccc ccgaccccac caggatctac agcctcagga cccccgtccc aatccttacc
241 ccttgcccca tcaccatctt catgcttacc tccacccccа tccgatcccc atccaggcag
301 aatccagttc caccctgcc cggaacccag ggtagtaccg ttgccaggat gtgacgccac
361 tgacttgcgc attggaggtc agaagaccgc gagattctcg ccctgagcaa cgagcgacgg
421 cctgacgtcg gcggagggaa gccggcccag gctcggtgag gaggcaaggt aagacgctga
481 gggaggactg aggcgggcct cacctcagac agagggcctc aaataatcca gtgctgcctc
541 tgctgccggg cctgggccac cccgcagggg aagacttcca ggctgggtcg ccactacctc

601 accccgccga cccccgccgc tttagccacg gggaactctg gggacagagc ttaatgtggc

661 cagggcaggg ctggttagaa gaggtcaggg cccacgctgt ggcaggaatc aaggtcagga

721 ccccgagagg gaactgaggg cagcctaacc accaccctca ccaccattcc cgtcccccaa

781 cacccaaccc cacccccatc ccccattccc atccccaccc ccacccctat cctggcagaa

841 tccgggcttt gcccctggta tcaagtcacg gaagctccgg gaatggcggc caggcacgtg

901 agtcctgagg ttcacatcta cggctaaggg agggaagggg ttcggtatcg cgagtatggc

961 cgttgggagg cagcgaaagg gcccaggcct cctggaagac agtggagtcc tgaggggacc

1021 cagcatgcca ggacaggggg cccactgtac ccctgtctca aaccgaggca ccttttcatt

1081 cggctacggg aatcctaggg atgcagaccc acttcagcag ggggttgggg cccagccctg

1141 cgaggagtca tggggaggaa gaagagggag gactgagggg accttggagt ccagatcagt

1201 ggcaaccttg ggctgggggа tgctgggcac agtggccaaa tgtgctctgt gctcattgcg

1261 ccttcagggt gaccagagag ttgagggctg tggtctgaag agtgggactt caggtcagca

1321 gagggaggaa tcccaggatc tgcagggccc aaggtgtacc cccaaggggc ccctatgtgg

1381 tggacagatg cagtggtcct aggatctgcc aagcatccag gtgaagagac tgagggagga

1441 ttgagggtac ccctgggaca gaatgcggac tgggggcccc ataaaaatct gccctgctcc

1501 tgctgttacc tcagagagcc tgggcagggc tgtcagctga ggtccctcca ttatcctagg

1561 atcactgatg tcagggaagg ggaagccttg gtctgagggg gctgcactca gggcagtaga

1621 gggaggctct cagaccctac taggagtgga ggtgaggacc aagcagtctc ctcacccagg

1681 gtacatggac ttcaataaat ttggacatct ctcgttgtcc tttccgggag gacctgggaa

1741 tgtatggcca gatgtgggtc ccctcatgtt tttctgtacc atatcaggta tgtgagttct

1801 tgacatgaga gattctcagg ccagcagaag ggagggatta ggccctataa ggagaaaggt

1861 gagggccctg agtgagcaca gaggggatcc tccaccccag tagagtgggg acctcacaga

1921 gtctggccaa ccctcctgac agttctggga atccgtggct gcgtttgctg tctgcacatt

1981 gggggcccgt ggattcctct cccaggaatc aggagctcca ggaacaaggc agtgaggact

2041 tggtctgagg cagtgtcctc aggtcacaga gtagaggggg ctcagatagt gccaacggtg

2101 aaggtttgcc ttggattcaa accaagggcc ccacctgccc cagaacacat ggactccaga

2161 gcgcctggcc tcaccctcaa tactttcagt cctgcagcct cagcatgcgc tggccggatg
2221 taccctgagg tgccctctca cttcctcctt caggttctga ggggacaggc tgacctggag
2281 gaccagaggc ccccggagga gcactgaagg agaagatctg taagtaagcc tttgttagag
2341 cctccaaggt tccattcagt actcagctga ggtctctcac atgctccctc tctccccagg
2401 ccagtgggtc tccattgccc agctcctgcc cacactcccg cctgttgccc tgaccagagt
2461 catcatgcct cttgagcaga ggagtcagca ctgcaagcct gaagaaggcc ttgaggcccg
2521 aggagaggcc ctgggcctgg tgggtgcgca ggctcctgct actgaggagc aggaggctgc
2581 ctcctcctct tctactctag ttgaagtcac cctgggggag gtgcctgctg ccgagtcacc
2641 agatcctccc cagagtcctc agggagcctc cagcctcccc actaccatga actaccctct
2701 ctggagccaa tcctatgagg actccagcaa ccaagaagag gaggggccaa gcaccttccc
2761 tgacctggag tccgagttcc aagcagcact cagtaggaag gtggccgagt tggttcattt
2821 tctgctcctc aagtatcgag ccagggagcc ggtcacaaag gcagaaatgc tggggagtgt
2881 cgtcggaaat tggcagtatt tctttcctgt gatcttcagc aaagcttcca gttccttgca
2941 gctggtcttt ggcatcgagc tgatggaagt ggaccccatc ggccacttgt acatctttgc
3001 cacctgcctg ggcctctcct acgatggcct gctgggtgac aatcagatca tgcccaaggc
3061 aggcctcctg ataatcgtcc tggccataat cgcaagagag ggcgactgtg cccctgagga
3121 gaaaatctgg gaggagctga gtgtgttaga ggtgtttgag gggagggaag acagtatctt
3181 gggggatccc aagaagctgc tcacccaaca tttcgtgcag gaaaactacc tggagtaccg
3241 gcaggtcccc ggcagtgatc ctgcatgtta tgaattcctg tggggtccaa gggccctcgt
3301 tgaaaccagc tatgtgaaag tcctgcacca tatggtaaag atcagtggag gacctcacat
3361 ttcctaccca cccctgcatg agtgggtttt gagagagggg gaagagtgag tctgagcacg
3421 agttgcagcc agggccagtg ggaggggtc tgggccagtg caccttccgg ggccgcatcc
3481 cttagtttcc actgcctcct gtgacgtgag gcccattctt cactctttga agcgagcagt
3541 cagcattctt agtagtgggt ttctgttctg ttggatgact ttgagattat tctttgtttc
3601 ctgttggagt tgttcaaatg ttccttttaa cggatggttg aatgagcgtc agcatccagg
3661 tttatgaatg acagtagtca cacatagtgc tgtttatata gtttaggagt aagagtcttg

3721 ttttttactc aaattgggaa atccattcca ttttgtgaat tgtgacataa taatagcagt
3781 ggtaaaagta tttgcttaaa attgtgagcg aattagcaat aacatacatg agataactca
3841 agaaatcaaa agatagttga ttcttgcctt gtacctcaat ctattctgta aaattaaaca
3901 aatatgcaaa ccaggatttc cttgacttct ttgagaatgc aagcgaaatt aaatctgaat
3961 aaataattct tcctcttcac tggctcgttt cttttccgtt cactcagcat ctgctctgtg
4021 ggaggccctg ggttagtagt ggggatgcta aggtaagcca gactcacgcc tacccatagg
4081 gctgtagagc ctaggacctg cagtcatata attaaggtgg tgagaagtcc tgtaagatgt
4141 agaggaaatg taagagaggg gtgagggtgt ggcgctccgg gtgagagtag tggagtgtca
4201 gtgc
//

Homo sapiens prostate stem cell antigen (PSCA) mRNA, complete cds.
ACCESSION AF043498
VERSION AF043498.1 GI:2909843
SEQ ID NO 79

/translation="MKAVLLALLMAGLALQPGTALLCYSCKAQVSNEDCLQVENCTQLGEQCW TARIRAVGLLTVISKGCSLNCVDDSQDYYVGKKNITCCDTDLCNASGAHALQPAAAILALLPA LGLLLWGPGQL"

SEQ ID NO 87
ORIGIN
1 agggagaggc agtgaccatg aaggctgtgc tgcttgccct gttgatggca ggcttggccc
61 tgcagccagg cactgccctg ctgtgctact cctgcaaagc ccaggtgagc aacgaggact
121 gcctgcaggt ggagaactgc acccagctgg gggagcagtg ctggaccgcg cgcatccgcg
181 cagttggcct cctgaccgtc atcagcaaag gctgcagctt gaactgcgtg gatgactcac
241 aggactacta cgtgggcaag aagaacatca cgtgctgtga caccgacttg tgcaacgcca
301 gcggggccca tgccctgcag ccggctgccg ccatccttgc gctgctccct gcactcggcc
361 tgctgctctg gggacccggc cagctatagg ctctgggggg ccccgctgca gcccacactg
421 ggtgtggtgc cccaggcctt tgtgccactc ctcacagaac ctggcccagt gggagcctgt
481 cctggttcct gaggcacatc ctaacgcaag tttgaccatg tatgtttgca ccccttttcc
541 ccnaaccctg accttcccat gggccttttc caggattccn accnggcaga tcagttttag

601 tganacanat ccgcntgcag atggcccctc caaccntttn tgttgntgtt tccatggccc
661 agcattttcc acccttaacc ctgtgttcag gcacttnttc ccccaggaag ccttccctgc
721 ccaccccatt tatgaattga gccaggtttg gtccgtggtg tcccccgcac ccagcagggg
781 acaggcaatc aggagggccc agtaaaggct gagatgaagt ggactgagta gaactggagg
841 acaagagttg acgtgagttc ctgggagttt ccagagatgg ggcctggagg cctggaggaa
901 ggggccaggc ctcacatttg tggggntccc gaatggcagc ctgagcacag cgtaggccct
961 taataaacac ctgttggata agccaaaaaa
//

GLANDULAR KALLIKREIN 1 PRECURSOR (TISSUE KALLIKREIN)
(KIDNEY/PANCREAS/SALIVARY GLAND KALLIKREIN).
ACCESSION P06870
PID g125170
VERSION P06870 GI:125170

SEQ ID NO 600
ORIGIN
1 mwflvlclal slggtgaapp iqsrivggwe ceqhsqpwqa alyhfstfqc ggilvhrqwv
61 ltaahcisdn yqlwlgrhnl fddentaqfv hvsesfphpg fnmsllenht rqadedyshd
121 lmllrltepa dtitdavkvv elptqepevg stclasgwgs iepenfsfpd dlqcvdlkil
181 pndecekahv qkvtdfmlcv ghleggkdtc vgdsggplmc dgvlqgvtsw gyvpcgtpnk
241 psvavrvlsy vkwiedtiae ns
//

ELASTASE 2A PRECURSOR.
ACCESSION P08217
PID g119255
VERSION P08217 GI:119255

SEQ ID NO 601
ORIGIN
1 mirtlllstl vagalscgdp typpyvtrvv ggeearpnsw pwqvslqyss ngkwyhtcgg
61 slianswvlt aahcisssrt yrvglgrhnl yvaesgslav svskivvhkd wnsnqiskgn
121 diallklanp vsltdkiqla clppagtilp nnypcyvtgw grlqtngavp dvlqqgrllv
181 vdyatcsssa wwgssvktsm icaggdgvis scngdsggpl ncqasdgrwq vhgivsfgsr
241 lgcnyyhkps vftrvsnyid winsviann

//

pancreatic elastase IIB [Homo sapiens].
ACCESSION NP_056933
PID g7705648
VERSION NP_056933.1 GI:7705648

SEQ ID NO 602
ORIGIN
1 mirtlllstl vagalscgvs tyapdmsrml ggeearpnsw pwqvslqyss
ngqwyhtcgg
61 slianswvlt aahcisssri yrvmlgqhnl yvaesgslav svskivvhkd
wnsnqvskgn
121 diallklanp vsltdkiqla clppagtilp nnypcyvtgw grlqtngalp
ddlkqgrllv
181 vdyatcsssg wwgstvktnm icaggdgvic tcngdsggpl ncqasdgrwe
vhgigsltsv
241 lgcnyyykps iftrvsnynd winsviann
//

PRAME Homo sapiens preferentially expressed antigen in melanoma (PRAME), mRNA.
ACCESSION NM_006115
VERSION NM_006115.1 GI:5174640
SEQ ID NO 77

/translation="MERRRLWGSIQSRYISMSVWTSPRRLVELAGQSLLKDEALAIAALELLPREL
FPPLFMAAFDGRHSQTLKAMVQAWPFTCLPLGVLMKGQHLHLETFKAVLDGLDVLLAQEVRPRRWK
LQVLDLRKNSHQDFWTVWSGNRASLYSFPEPEAAQPMTKKRKVDGLSTEAEQPFIPVEVLVDLFLK
EGACDELFSYLIEKVKRKKNVLRLCCKKLKIFAMPMQDIKMILKMVQLDSIEDLEVTCTWKLPTLA
KFSPYLGQMINLRRLLLSHIHASSYISPEKEEQYIAQFTSQFLSLQCLQALYVDSLFFLRGRLDQL
LRHVMNPLETLSITNCRLSEGDVMHLSQSPSVSQLSVLSLSGVMLTDVSPEPLQALLERASATLQD
LVFDECGITDDQLLALLPSLSHCSQLTTLSFYGNSISISALQSLLQHLIGLSNLTHVLYPVPLESY
EDIHGTLHLERLAYLHARLRELLCELGRPSMVWLSANPCPHCGDRTFYDPEPILCPCFMPN"

SEQ ID NO 85
ORIGIN
1 gcttcagggt acagctcccc cgcagccaga agccgggcct gcagcccctc
agcaccgctc
61 cgggacaccc cacccgcttc ccaggcgtga cctgtcaaca gcaacttcgc
ggtgtggtga
121 actctctgag gaaaaaccat tttgattatt actctcagac gtgcgtggca
acaagtgact
181 gagacctaga aatccaagcg ttggaggtcc tgaggccagc ctaagtcgct
tcaaaatgga
241 acgaaggcgt ttgtggggtt ccattcagag ccgatacatc agcatgagtg
tgtggacaag
301 cccacggaga cttgtggagc tggcagggca gagcctgctg aaggatgagg
ccctggccat
361 tgccgccctg gagttgctgc ccagggagct cttcccgcca ctcttcatgg
cagcctttga

421 cgggagacac agccagaccc tgaaggcaat ggtgcaggcc tggcccttca cctgcctccc
481 tctgggagtg ctgatgaagg gacaacatct tcacctggag accttcaaag ctgtgcttga
541 tggacttgat gtgctccttg cccaggaggt tcgccccagg aggtggaaac ttcaagtgct
601 ggatttacgg aagaactctc atcaggactt ctggactgta tggtctggaa acagggccag
661 tctgtactca tttccagagc cagaagcagc tcagcccatg acaaagaagc gaaaagtaga
721 tggtttgagc acagaggcag agcagccctt cattccagta gaggtgctcg tagacctgtt
781 cctcaaggaa ggtgcctgtg atgaattgtt ctcctacctc attgagaaag tgaagcgaaa
841 gaaaaatgta ctacgcctgt gctgtaagaa gctgaagatt tttgcaatgc ccatgcagga
901 tatcaagatg atcctgaaaa tggtgcagct ggactctatt gaagatttgg aagtgacttg
961 tacctggaag ctacccacct tggcgaaatt ttctccttac ctgggccaga tgattaatct
1021 gcgtagactc ctcctctccc acatccatgc atcttcctac atttccccgg agaaggaaga
1081 gcagtatatc gcccagttca cctctcagtt cctcagtctg cagtgcctgc aggctctcta
1141 tgtggactct ttatttttcc ttagaggccg cctggatcag ttgctcaggc acgtgatgaa
1201 ccccttggaa accctctcaa taactaactg ccggctttcg gaaggggatg tgatgcatct
1261 gtcccagagt cccagcgtca gtcagctaag tgtcctgagt ctaagtgggg tcatgctgac
1321 cgatgtaagt cccgagcccc tccaagctct gctggagaga gcctctgcca ccctccagga
1381 cctggtcttt gatgagtgtg ggatcacgga tgatcagctc cttgccctcc tgccttccct
1441 gagccactgc tcccagctta caaccttaag cttctacggg aattccatct ccatatctgc
1501 cttgcagagt ctcctgcagc acctcatcgg gctgagcaat ctgacccacg tgctgtatcc
1561 tgtccccctg gagagttatg aggacatcca tggtaccctc cacctggaga ggcttgccta
1621 tctgcatgcc aggctcaggg agttgctgtg tgagttgggg cggcccagca tggtctggct
1681 tagtgccaac ccctgtcctc actgtgggga cagaaccttc tatgacccgg agcccatcct
1741 gtgcccctgt ttcatgccta actagctggg tgcacatatc aaatgcttca ttctgcatac
1801 ttggacacta aagccaggat gtgcatgcat cttgaagcaa caaagcagcc acagtttcag
1861 acaaatgttc agtgtgagtg aggaaaacat gttcagtgag gaaaaaacat tcagacaaat
1921 gttcagtgag gaaaaaaagg ggaagttggg gataggcaga tgttgacttg aggagttaat

1981 gtgatctttg gggagataca tcttatagag ttagaaatag aatctgaatt tctaaaggga
2041 gattctggct tgggaagtac atgtaggagt taatccctgt gtagactgtt gtaaagaaac
2101 tgttgaaaat aaagagaagc aatgtgaagc aaaaaaaaaa aaaaaaaa

ED-B domain of Fibronectin

Human fibronectin gene ED-B region.

ACCESSION X07717

VERSION X07717.1 GI:31406

SEQ ID NO 590

/translation="CTFDNLSPGLEYNVSVYTVKDDKESVPISDTIIPEVPQLTDLSF

VDITDSSIGLRWTPLNSSTIIGYRITVVAAGEGIPIFEDFVDSSVGYYTVTGLEPGID

YDISVITLINGGESAPTTLTQQTAVPPPTDLRFTNIGPDTMRVTW"

SEQ ID NO 591

ORIGIN

1 ctgcactttt gataacctga gtcccggcct ggagtacaat gtcagtgttt acactgtcaa
61 ggatgacaag gaaagtgtcc ctatctctga taccatcatc ccaggtaata gaaaataagc
121 tgctatcctg agagtgacat tccaataaga gtggggatta gcatcttaat ccccagatgc
181 ttaagggtgt caactatatt tgggatttaa ttccgatctc ccagctgcac tttccaaaac
241 caagaagtca aagcagcgat ttggacaaaa tgcttgctgt taacactgct ttactgtctg
301 tgcttcactg ggatgctgtg tgttgcagcg agtatgtaat ggagtggcag ccatggcttt
361 aactctgtat tgtctgctca catggaagta tgactaaaac actgtcacgt gtctgtactc
421 agtactgata ggctcaaagt aatatggtaa atgcatccca tcagtacatt tctgcccgat

481 tttacaatcc atatcaattt ccaacagctg cctatttcat cttgcagttt caaatccttc

541 tttttgaaaa ttggatttta aaaaaaagtt aagtaaaagt cacaccttca gggttgttct

601 ttcttgtggc cttgaaagac aacattgcaa aggcctgtcc taaggatagg cttgtttgtc

661 cattgggtta taacataatg aaagcattgg acagatcgtg tccccctttg gactcttcag

721 tagaatgctt ttactaacgc taattacatg ttttgattat gaatgaacct aaaatagtgg

781 caatggcctt aacctaggcc tgtctttcct cagcctgaat gtgcttttga atggcacatt

841 tcacaccata cattcataat gcattagcgt tatggccatg atgttgtcat gagttttgta

901 tgggagaaaa aaaatcaatt tatcacccat ttattatttt ttccggttgt tcatgcaagc

961 ttattttcta ctaaaacagt tttggaatta ttaaaagcat tgctgatact tacttcagat

1021 attatgtcta ggctctaaga atggtttcga catcctaaac agccatatga tttttaggaa

1081 tctgaacagt tcaaattgta ccctttaagg atgttttcaa aatgtaaaaa atatatatat

1141 atatatatat tccctaaaag aatattcctg tttattcttc tagggaagca aactgttcat

1201 gatgcttagg aagtcttttc agagaattta aaacagattg catattacca tcattgcttt

1261 aacattccac caattttact actagtaacc tgatatacac tgctttattt tttcctcttt

1321 ttttccctct attttccttt tgcctccccc tccctttgct ttgtaactca atagaggtgc

1381 cccaactcac tgacctaagc tttgttgata taaccgattc aagcatcggc ctgaggtgga

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1501 gtatccctat ttttgaagat tttgtggact cctcagtagg atactacaca gtcacagggc

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1681 gatggtgttg catgctgcca ccagttactc cggttaaata tggatgtttc atgggggaag

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2401 agtactgcta tgtttctctt tgctgtgtgg caacttaagc ctcttcggcc tgggataaaa

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2521 ctttttttaaa tatatcaatg atggcaaaaa ggttaaaggg ggcctaacag tactgtgtgt

2581 agtgttttat ttttaacagt agtacactat aacttaaaat agacttagat tagactgttt

2641 gcatgattat gattctgttt cctttatgca tgaaatattg attttacctt tccagctact

2701 tcgttagctt taattttaaa atacattaac tgagtcttcc ttcttgttcg aaaccagctg

2761 ttcctcctcc cactgacctg cgattcacca acattggtcc agacaccatg cgtgtcacct

2821 ggg

//

CEA Homo sapiens carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5), mRNA.

ACCESSION NM_004363

VERSION NM_004363.1 GI:11386170

SEQ ID NO 592

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RAYVCGIQNSVSANRSDPVTLDVLYGPDTPIISPPDSSYLSGANLNLSCHSASNPSPQ
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SEQ ID NO 593

ORIGIN

1 ctcagggcag agggaggaag gacagcagac cagacagtca cagcagcctt gacaaaacgt

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241 ttcaatgtcg cagaggggaa ggaggtgctt ctacttgtcc acaatctgcc ccagcatctt

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1081 cccaaaccct tcatcaccag caacaactcc aaccccgtgg aggatgagga tgctgtagcc

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2761 ttcccagatt tcaggaaact ttttttcttt taagctatcc actcttacag caatttgata

2821 aaatatactt ttgtgaacaa aaattgagac atttacattt tctccctatg tggtcgctcc

2881 agacttggga aactattcat gaatatttat attgtatggt aatatagtta ttgcacaagt

2941 tcaataaaaa tctgctcttt gtataacaga aaaa

//

Her2/Neu Human tyrosine kinase-type receptor (HER2) mRNA, complete cds.

ACCESSION M11730

VERSION M11730.1 GI:183986

SEQ ID NO 594

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SEQ ID NO 595

ORIGIN Chromosome 17q21-q22.

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3181 gacgatgaca tgggggacct ggtggatgct gaggagtatc tggtacccca gcagggcttc

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4381 tgcttttctg tttagttttt acttttttg ttttgttttt ttaaagacga aataaagacc

4441 caggggagaa tgggtgttgt atggggaggc aagtgtgggg ggtccttctc cacacccact

4501 ttgtccattt gcaaatatat tttggaaaac

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H.sapiens mRNA for SCP1 protein.

ACCESSION X95654

VERSION X95654.1 GI:1212982

SEQ ID NO 596

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KLFV"

SEQ ID NO 597

ORIGIN

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421 gtataaggag gctgaaaaga taaaaaaatg gaaagtaagt acagaagctg aactgagaca

481 gaaagaaagt aagttgcaag aaaacagaaa gataattgaa gcacagcgaa aagccattca

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1081 gtcattacaa agaagtgtga gtactcaaaa ggctttagag gaagatttac agatagcaac

1141 aaaaacaatt tgtcagctaa ctgaagaaaa agaaactcaa atggaagaat ctaataaagc

1201 tagagctgct cattcgtttg tggttactga atttgaaact actgtctgca gcttggaaga

1261 attattgaga acagaacagc aaagattgga aaaaaatgaa gatcaattga aaatacttac

1321 catggagctt caaaagaaat caagtgagct ggaagagatg actaagctta caaataacaa

1381 agaagtagaa cttgaagaat tgaaaaaagt cttgggagaa aaggaaacac ttttatatga

1441 aaataaacaa tttgagaaga ttgctgaaga attaaaagga acagaacaag aactaattgg

1501 tcttctccaa gccagagaga aagaagtaca tgatttggaa atacagttaa ctgccattac

1561 cacaagtgaa cagtattatt caaaagaggt taaagatcta aaaactgagc ttgaaaacga

1621 gaagcttaag aatactgaat taacttcaca ctgcaacaag ctttcactag aaaacaaaga

1681 gctcacacag gaaacaagtg atatgaccct agaactcaag aatcagcaag aagatattaa

1741 taataacaaa aagcaagaag aaaggatgtt gaaacaaata gaaaatcttc aagaaacaga

1801 aacccaatta agaaatgaac tagaatatgt gagagaagag ctaaaacaga aaagagatga

1861 agttaaatgt aaattggaca agagtgaaga aaattgtaac aatttaagga aacaagttga

1921 aaataaaaac aagtatattg aagaacttca gcaggagaat aaggccttga aaaaaaaagg

1981 tacagcagaa agcaagcaac tgaatgttta tgagataaag gtcaataaat tagagttaga

2041 actagaaagt gccaaacaga aatttggaga aatcacagac acctatcaga aagaaattga

2101 ggacaaaaag atatcagaag aaaatctttt ggaagaggtt gagaaagcaa aagtaatagc

2161 tgatgaagca gtaaaattac agaaagaaat tgataagcga tgtcaacata aaatagctga

2221 aatggtagca cttatggaaa aacataagca ccaatatgat aagatcattg aagaaagaga

2281 ctcagaatta ggactttata agagcaaaga acaagaacag tcatcactga gagcatcttt

2341 ggagattgaa ctatccaatc tcaaagctga acttttgtct gttaagaagc aacttgaaat

2401 agaaagagaa gagaaggaaa aactcaaaag agaggcaaaa gaaaacacag ctactcttaa

2461 agaaaaaaaa gacaagaaaa cacaaacatt tttattggaa acacctgaaa tttattggaa

2521 attggattct aaagcagttc cttcacaaac tgtatctcga aatttcacat cagttgatca

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2641 accattgcca aaggcatata cagtgaagac accaacaaaa ccaaaactac agcaaagaga

2701 aaacttgaat atacccattg aagaaagtaa aaaaaagaga aaaatggcct ttgaatttga

2761 tattaattca gatagttcag aaactactga tcttttgagc atggtttcag aagaagagac

2821 attgaaaaca ctgtatagga acaataatcc accagcttct catctttgtg tcaaaacacc

2881 aaaaaaggcc ccttcatctc taacaacccc tggacctaca ctgaagtttg gagctataag

2941 aaaaatgcgg gaggaccgtt gggctgtaat tgctaaaatg gatagaaaaa aaaaactaaa

3001 agaagctgaa aagttatttg tttaatttca gagaatcagt gtagttaagg agcctaataa

3061 cgtgaaactt atagttaata ttttgttctt atttgccaga gccacatttt atctggaagt

3121 tgagacttaa aaaatacttg catgaatgat ttgtgtttct ttatattttt agcctaaatg

3181 ttaactacat attgtctgga aacctgtcat tgtattcaga taattagatg attatatatt

3241 gttgttactt tttcttgtat tcatgaaaac tgtttttact aagttttcaa atttgtaaag

3301 ttagcctttg aatgctagga atgcattatt gagggtcatt ctttattctt tactattaaa

3361 atattttgga tgcaaaaaaa aaaaaaaaaa aaa

//

Homo sapiens synovial sarcoma, X breakpoint 4 (SSX4), mRNA.

ACCESSION NM_005636

VERSION NM_005636.1 GI:5032122

SEQ ID NO 598

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SEQ ID NO 599

ORIGIN

1 atgaacggag acgacgcctt tgcaaggaga cccagggatg atgctcaaat atcagagaag

61 ttacgaaagg ccttcgatga tattgccaaa tacttctcta agaaagagtg ggaaaagatg

121 aaatcctcgg agaaaatcgt ctatgtgtat atgaagctaa actatgaggt catgactaaa

181 ctaggtttca aggtcaccct cccacctttc atgcgtagta aacgggctgc agacttccac

241 gggaatgatt ttggtaacga tcgaaaccac aggaatcagg ttgaacgtcc tcagatgact

301 ttcggcagcc tccagagaat cttcccgaag atcatgccca agaagccagc agaggaagaa

361 aatggtttga aggaagtgcc agaggcatct ggcccacaaa atgatgggaa acagctgtgc

421 cccccgggaa atccaagtac cttggagaag attaacaaga catctggacc caaaaggggg

481 aaacatgcct ggacccacag actgcgtgag agaaagcagc tggtggttta tgaagagatc

541 agcgaccctg aggaagatga cgagtaactc ccctcg

All patents and publications mentioned in the specification are indicative of the levels of those skilled in the art to which the invention pertains.

The invention illustratively described herein suitably may be practiced in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions indicates the exclusion of equivalents of the features shown and described or portions thereof. It is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the appended claims.

WHAT IS CLAIMED IS:

1. An isolated epitope, comprising a component selected from the group consisting of:

(i) a polypeptide having the sequence as disclosed in TABLE 1;

(ii) an epitope cluster comprising the polypeptide of (i);

(iii) a polypeptide having substantial similarity to (i) or (ii);

(iv) a polypeptide having functional similarity to any of (i) through (iii); and

(v) a nucleic acid encoding the polypeptide of any of (i) through (iv).

2. The epitope of claim 1, wherein the epitope is immunologically active.

3. The epitope of claim 1, wherein the polypeptide is less than about 30 amino acids in length.

4. The epitope of claim 1, wherein the polypeptide is 8 to 10 amino acids in length.

5. The epitope of claim 1, wherein the substantial or functional similarity comprises addition of at least one amino acid.

6. The epitope of claim 5, wherein the at least one additional amino acid is at an N-terminus of the polypeptide.

7. The epitope of claim 1, wherein the substantial or functional similarity comprises a substitution of at least one amino acid.

8. The epitope of claim 1, the polypeptide having affinity to an HLA-A2 molecule.

9. The epitope of claim 8, wherein the affinity is determined by an assay of binding.

10. The epitope of claim 8, wherein the affinity is determined by an assay of restriction of epitope recognition.

11. The epitope of claim 8, wherein the affinity is determined by a prediction algorithm.

12. The epitope of claim 1, the polypeptide having affinity to an HLA-B7 or HLA-B51 molecule.

13. The epitope of claim 1, wherein the polypeptide is a housekeeping epitope.

14. The epitope of claim 1, wherein the polypeptide corresponds to an epitope displayed on a tumor cell.

15. The epitope of claim 1, wherein the polypeptide corresponds to an epitope displayed on a neovasculature cell.

16. The epitope of claim 1, wherein the polypeptide is an immune epitope.

17. The epitope of claim 1 wherein the epitope is a nucleic acid.

18. A pharmaceutical composition comprising the polypeptide of claim 1 and a pharmaceutically acceptable adjuvant, carrier, diluent, or excipient.

19. The composition of claim 18, where the adjuvant is a polynucleotide.

20. The composition of claim 19 wherein the polynucleotide comprises a dinucleotide.

21. The composition of claim 20 wherein the dinucleotide is CpG.

22. The composition of claim 18, wherein the adjuvant is encoded by a polynucleotide.

23. The composition of claim 18 wherein the adjuvant is a cytokine.

24. The composition of claim 23 wherein the cytokine is GM-CSF.

25. The composition of claim 18 further comprising a professional antigen-presenting cell (pAPC).

26. The composition of claim 25, wherein the pAPC is a dendritic cell.

27. The composition of claim 18, further comprising a second epitope.

28. The composition of claim 27, wherein the second epitope is a polypeptide.

29. The composition of claim 27, wherein the second epitope is a nucleic acid.

30. The composition of claim 27, wherein the second epitope is a housekeeping epitope.

31. The composition of claim 27, wherein the second epitope is an immune epitope.

32. A pharmaceutical composition comprising the nucleic acid of claim 1 and a pharmaceutically acceptable adjuvant, carrier, diluent, or excipient.

33. A recombinant construct comprising the nucleic acid of Claim 1.

34. The construct of claim 33, further comprising a plasmid, a viral vector, or an artificial chromosome.

35. The construct of claim 33, further comprising a sequence encoding at least one feature selected from the group consisting of a second epitope, an IRES, an ISS, an NIS, and ubiquitin.

36. A purified antibody that specifically binds to the epitope of claim 1.

37. A purified antibody that specifically binds to a peptide-MHC protein complex comprising the epitope of claim 1.

38. The antibody of claim 36 or claim 37, wherein the antibody is a monoclonal antibody.

39. A multimeric MHC-peptide complex comprising the epitope of claim 1.

40. An isolated T cell expressing a T cell receptor specific for an MHC-peptide complex, the complex comprising the epitope of claim 1.

41. The T cell of claim 40, produced by an *in vitro* immunization.

42. The T cell of claim 40, isolated from an immunized animal.

43. A T cell clone comprising the T cell of claim 40.

44. A polyclonal population of T cells comprising the T cell of claim 40.

45. A pharmaceutical composition comprising the T cell of claim 40 and a pharmaceutically acceptable adjuvant, carrier, diluent, or excipient.

46. An isolated protein molecule comprising the binding domain of a T cell receptor specific for an MHC-peptide complex, the complex comprising the epitope of claim 1.

47. The protein of claim 46, wherein the protein is multivalent.

48. An isolated nucleic acid encoding the protein of claim 46.

49. A recombinant construct comprising the nucleic acid of claim 48.

50. A host cell expressing the recombinant construct, the construct comprising the nucleic acid of claim 1, or the construct encoding a protein molecule comprising the binding domain of a T cell receptor specific for an MHC-peptide complex.

51. The host cell of claim 50, wherein the host cell is a dendritic cell, macrophage, tumor cell, or tumor-derived cell.

52. The host cell of claim 50, wherein the host cell is a bacterium, fungus, or protozoan.

53. A pharmaceutical composition comprising the host cell of claim 50 and a pharmaceutically acceptable adjuvant, carrier, diluent, or excipient.

54. A vaccine or immunotherapeutic composition comprising at least one component selected from the group consisting of the epitope of claim 1; the composition of claim 18, 32, or 45, the construct of claim 33; the T cell of claim 40, a host cell expressing a recombinant construct comprising a nucleic acid encoding a T cell receptor binding domain specific for an MHC-peptide complex and a composition comprising the same, and a host cell expressing a recombinant construct comprising the nucleic acid of claim 1 and a composition comprising the same.

55. A method of treating an animal, comprising:

administering to an animal the vaccine or immunotherapeutic composition of claim 54.

56. The method of claim 55, wherein the administering step comprises a mode of delivery selected from the group consisting of transdermal, intranodal, perinodal, oral, intravenous, intradermal, intramuscular, intraperitoneal, mucosal, aerosol inhalation, and instillation.

57. The method of claim 55, further comprising a step of assaying to determine a characteristic indicative of a state of a target cell or target cells.

58. The method of claim 57, comprising a first assaying step and a second assaying step, wherein the first assaying step precedes the administering step, and wherein the second assaying step follows the administering step.

59. The method of claim 58, further comprising a step of comparing the characteristic determined in the first assaying step with the characteristic determined in the second assaying step to obtain a result.

60. The method of claim 59, wherein the result is selected from the group consisting of: evidence of an immune response, a diminution in number of target cells, a loss of mass or size of a tumor comprising target cells, a decrease in number or concentration of an intracellular parasite infecting target cells.

61. A method of evaluating immunogenicity of a vaccine or immunotherapeutic composition, comprising:

administering to an animal the vaccine or immunotherapeutic composition of claim 54; and

evaluating immunogenicity based on a characteristic of the animal.

62. The method of claim 61, wherein the animal is HLA-transgenic.

63. A method of evaluating immunogenicity , comprising:

in vitro stimulation of a T cell with the vaccine or immunotherapeutic composition of claim 54; and

evaluating immunogenicity based on a characteristic of the T cell.

64. The method of claim 63, wherein the stimulation is a primary stimulation.

65. A method of making a passive/adoptive immunotherapeutic, comprising:

combining the T cell of claim 40, or a host cell expressing a recombinant construct comprising a nucleic acid encoding a T cell receptor binding domain specific for an MHC-peptide complex, or a host cell expressing a recombinant construct comprising the nucleic acid of claim 1 with a pharmaceutically acceptable adjuvant, carrier, diluent, or excipient.

66. A method of determining specific T cell frequency comprising the step of contacting T cells with a MHC-peptide complex comprising the epitope of claim 1.

67. The method of claim 66, wherein the contacting step comprises at least one feature selected from the group consisting of immunization, restimulation, detection, and enumeration.

68. The method of Claim 66, further comprising ELISPOT analysis, limiting dilution analysis, flow cytometry, in situ hybridization, the polymerase chain reaction or any combination thereof.

69. A method of evaluating immunologic response, comprising the method of claim 66 carried out prior to and subsequent to an immunization step.

70. A method of evaluating immunologic response, comprising:

determining frequency, cytokine production, or cytolytic activity of T cells, prior to and subsequent to a step of stimulation with MHC-peptide complexes comprising the epitope of claim 1.

71. A method of diagnosing a disease comprising:

contacting a subject tissue with at least one component selected from the group consisting of the T cell of claim 40, the host cell of claim 50, the antibody of claim 36, and the protein of claim 46; and

diagnosing the disease based on a characteristic of the tissue or of the component.

72. The method of claim 71, wherein the contacting step takes place *in vivo*.

73. The method of claim 71, wherein the contacting step takes place *in vitro*.

74. A method of making a vaccine, comprising:

combining at least one component selected from the group consisting of the epitope of claim 1; the composition of claim 18, 32, 45, or 53; the construct of claim 33; the T cell of claim 40, and the host cell of claim 50, with a pharmaceutically acceptable adjuvant, carrier, diluent, or excipient.

75. A computer readable medium having recorded thereon the sequence of any one of SEQ ID NOS: 1-602, in a machine having a hardware or software that calculates the physical, biochemical, immunologic, or molecular genetic properties of a molecule embodying said sequence.

76. A method of treating an animal comprising combining the method of claim 55 combined with at least one mode of treatment selected from the group of radiation therapy, chemotherapy, biochemotherapy, and surgery.

77. An isolated polypeptide comprising an epitope cluster from a target-associated antigen having the sequence as disclosed in Tables 25-44, wherein the amino acid sequence consists of not more than about 80% of the amino acid sequence of the antigen.

78. A vaccine or immunotherapeutic product comprising the polypeptide of claim 78.

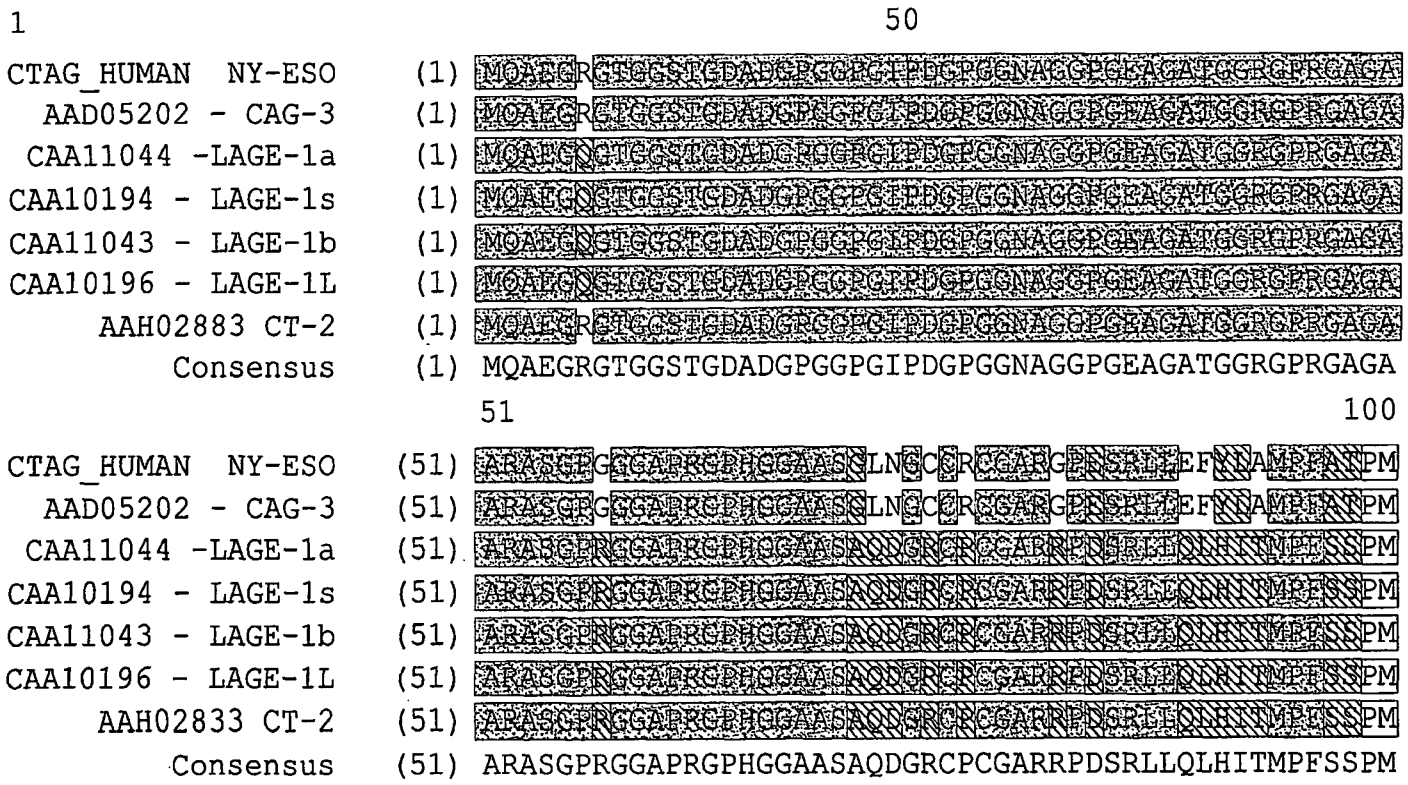
79. An isolated polynucleotide encoding the polypeptide of claim 78.

80. A vaccine or immunotherapeutic product comprising the polynucleotide of claim 80.

81. The polynucleotide of claim 79 or 80, wherein the polynucleotide is DNA.

82. The polynucleotide of claim 79 or 80, wherein the polynucleotide is RNA.

FIG. 1A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50
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CAA11044 -LAGE-1a (1) MQAEGQGTGGSTGDADGPGGPGIPDGPGGNAGGPGEAGATGGRGPRGAGA
CAA10194 - LAGE-1s (1) MQAEGQGTGGSTGDADGPGGPGIPDGPGGNAGGPGEAGATGGRGPRGAGA
CAA11043 - LAGE-1b (1) MQAEGQGTGGSTGDADGPGGPGIPDGPGGNAGGPGEAGATGGRGPRGAGA
CAA10196 - LAGE-1L (1) MQAEGQGTGGSTGDADGPGGPGIPDGPGGNAGGPGEAGATGGRGPRGAGA
AAH02883 CT-2 (1) MQAEGRGTGGSTGDADGPGGPGIPDGPGGNAGGPGEAGATGGRGPRGAGA
Consensus (1) MQAEGRGTGGSTGDADGPGGPGIPDGPGGNAGGPGEAGATGGRGPRGAGA
51
100
CTAG_HUMAN NY-ESO (51) ARASGPRGGAPRGPHGGAASQLNGCPRCGARGPESRLLEFYLAMPFATPM
AAD05202 - CAG-3 (51) ARASGPRGGAPRGPHGGAASQLNGCPRCGARGPESRLLEFYLAMPFATPM
CAA11044 -LAGE-1a (51) ARASGPRGGAPRGPHGGAASAQDGRCPCGARRPDSRLLQLHITMPFSSPM
CAA10194 - LAGE-1s (51) ARASGPRGGAPRGPHGGAASAQDGRCPCGARRPDSRLLQLHITMPFSSPM
CAA11043 - LAGE-1b (51) ARASGPRGGAPRGPHGGAASAQDGRCPCGARRPDSRLLQLHITMPFSSPM
CAA10196 - LAGE-1L (51) ARASGPRGGAPRGPHGGAASAQDGRCPCGAPRPDSRLLQLHITMPFSSPM
AAH02833 CT-2 (51) ARASGPRGGAPRGPHGGAASAQDGRCPCGARRPDSRLLQLHITMPFSSPM
Consensus (51) ARASGPRGGAPRGPHGGAASAQDGRCPCGARRPDSRLLQLHITMPFSSPM

FIG. 1B

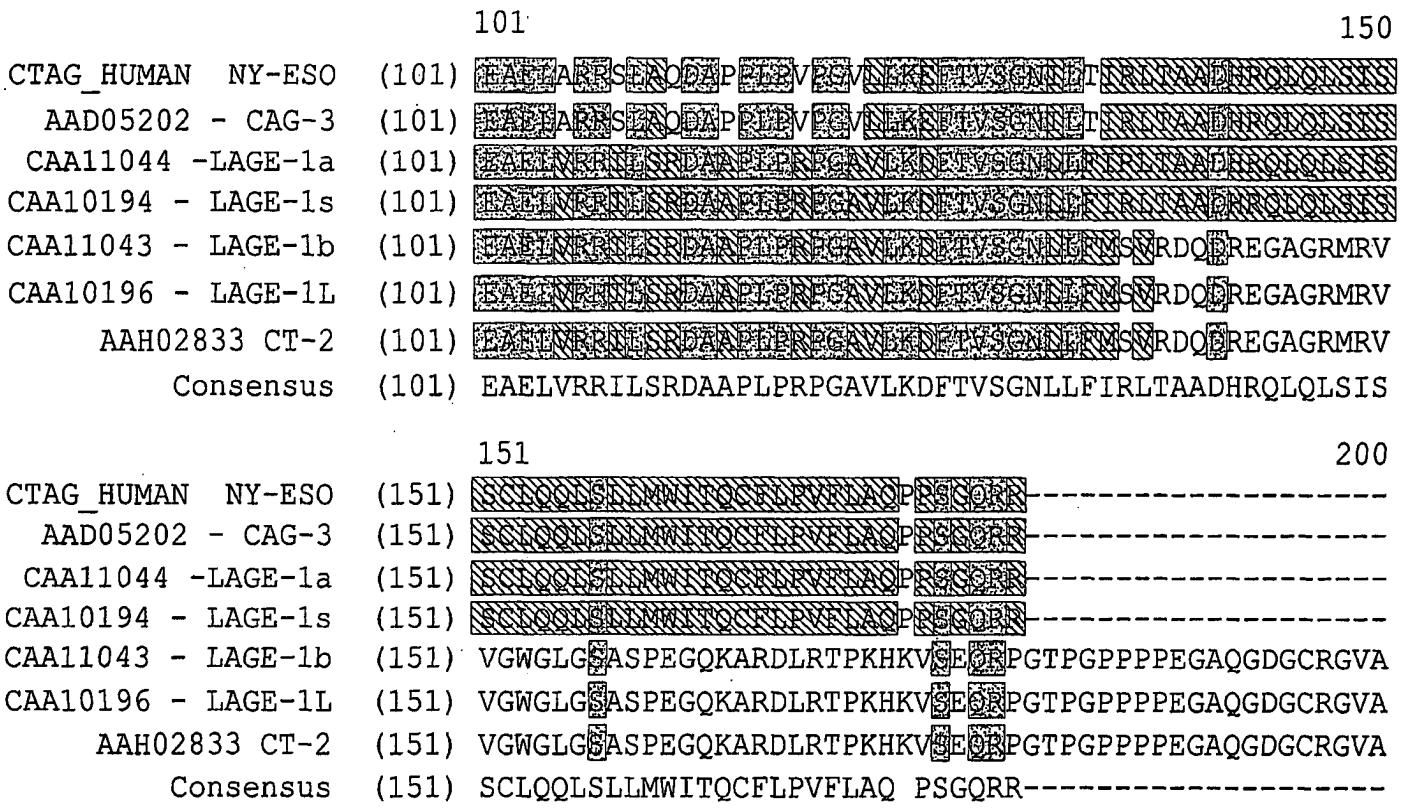
101
150
CTAG_HUMAN NY-ESO (101) EAELVRRILSRDAAPLPRPGAVLKDFTVSGNLLFIRLTAADHRQLQLSIS
AAD05202 - CAG-3 (101) EAELVRRILSRDAAPLPRPGAVLKDFTVSGNLLFIRLTAADHRQLQLSIS
CAA11044 -LAGE-1a (101) EAELVRRILSRDAAPLPRPGAVLKDFTVSGNLLFIRLTAADHRQLQLSIS
CAA10194 - LAGE-1s (101) EAELVRRILSRDAAPLPRPGAVLKDFTVSGNLLFIRLTAADHRQLQLSIS
CAA11043 - LAGE-1b (101) EAELVRRILSRDAAPLPRPGAVLKDFTVSGNLLFMSVRDQDREGAGRMRV
CAA10196 - LAGE-1L (101) EAELVRRILSRDAAPLPRPGAVLKDFTVSGNLLFMSVRDQDREGAGRMRV
AAH02833 CT-2 (101) EAELVRRILSRDAAPLPRPGAVLKDFTVSGNLLFMSVRDQDREGAGRMRV
Consensus (101) EAELVRRILSRDAAPLPRPGAVLKDFTVSGNLLFIRLTAADHRQLQLSIS
151
200
CTAG_HUMAN NY-ESO (151) SCLQQLSLLMWITQCFLPVFLAQPPSGQRR----------
AAD05202 - CAG-3 (151) SCLQQLSLLMWITQCFLPVFLAQPPSGQRR----------
CAA11044 -LAGE-1a (151) SCLQQLSLLMWITQCFLPVFLAQPPSGQRR----------
CAA10194 - LAGE-1s (151) SCLQQLSLLMWITQCFLPVFLAQPPEGQRR----------
CAA11043 - LAGE-1b (151) VGWGLGSASPEGQKARDLRTPKHKVSEQRPGTPGPPPPEGAQGDGCRGVA
CAA10196 - LAGE-1L (151) VGWGLGSASPEGQKARDLRTPKHKVSEQRPGTPGPPPPEGAQGDGCRGVA
AAH02833 CT-2 (151) VGWGLGSASPEGQKARDLRTPKHKVSEQRPGTPGPPPPEGAQGDGCRGVA
Consensus (151) SCLQQLSLLMWITQCFLPVFLAQ PSGQRR----------

FIG. 1C

```
                                  201
CTAG_HUMAN  NY-ESO   (181) ----------
  AAD05202 - CAG-3   (181) ----------
 CAA11044 -LAGE-1a   (181) ----------
CAA10194 - LAGE-1s   (181) ----------
CAA11043 - LAGE-1b   (201) FNVMFSAPHI
CAA10196 - LAGE-1L   (201) FNVMFSAPHI
     AAH02833 CT-2   (201) FNVMFSAPHI
         Consensus   (201)
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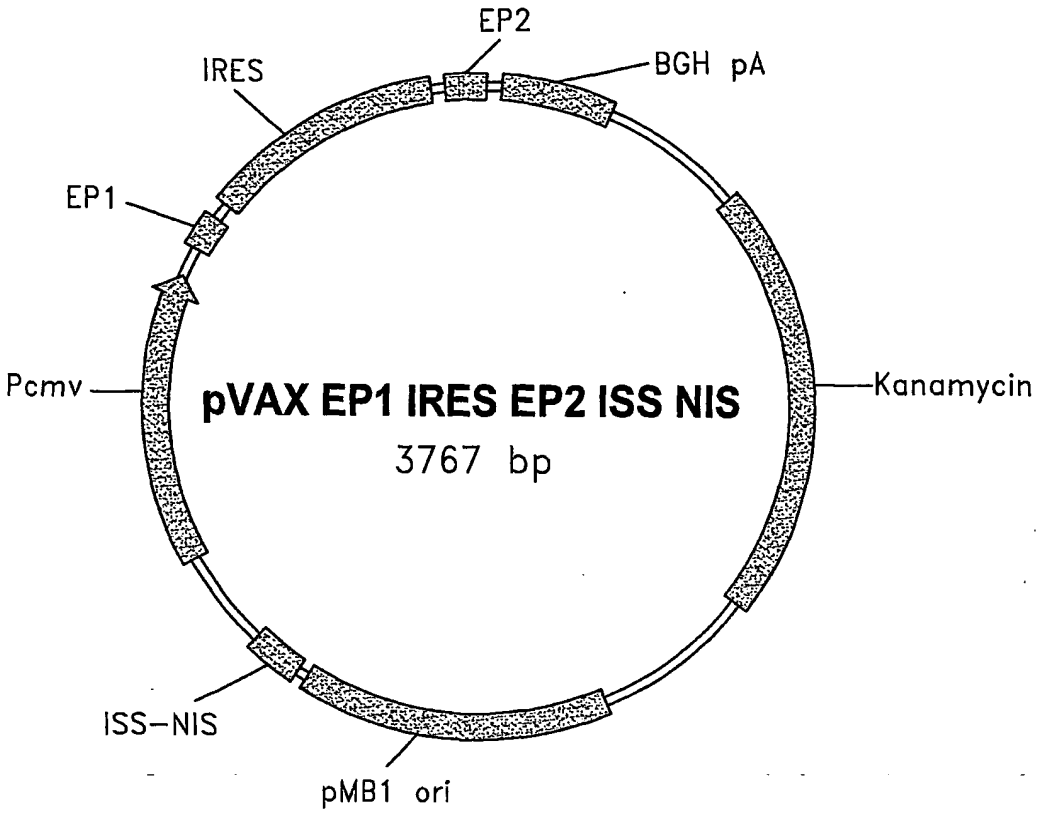

EP2
IRES
BGH pA
EP1
Pcmv
pVAX EP1 IRES EP2 ISS NIS
3767 bp
Kanamycin
ISS-NIS
pMB1 ori

FIG. 2

FIG. 3A

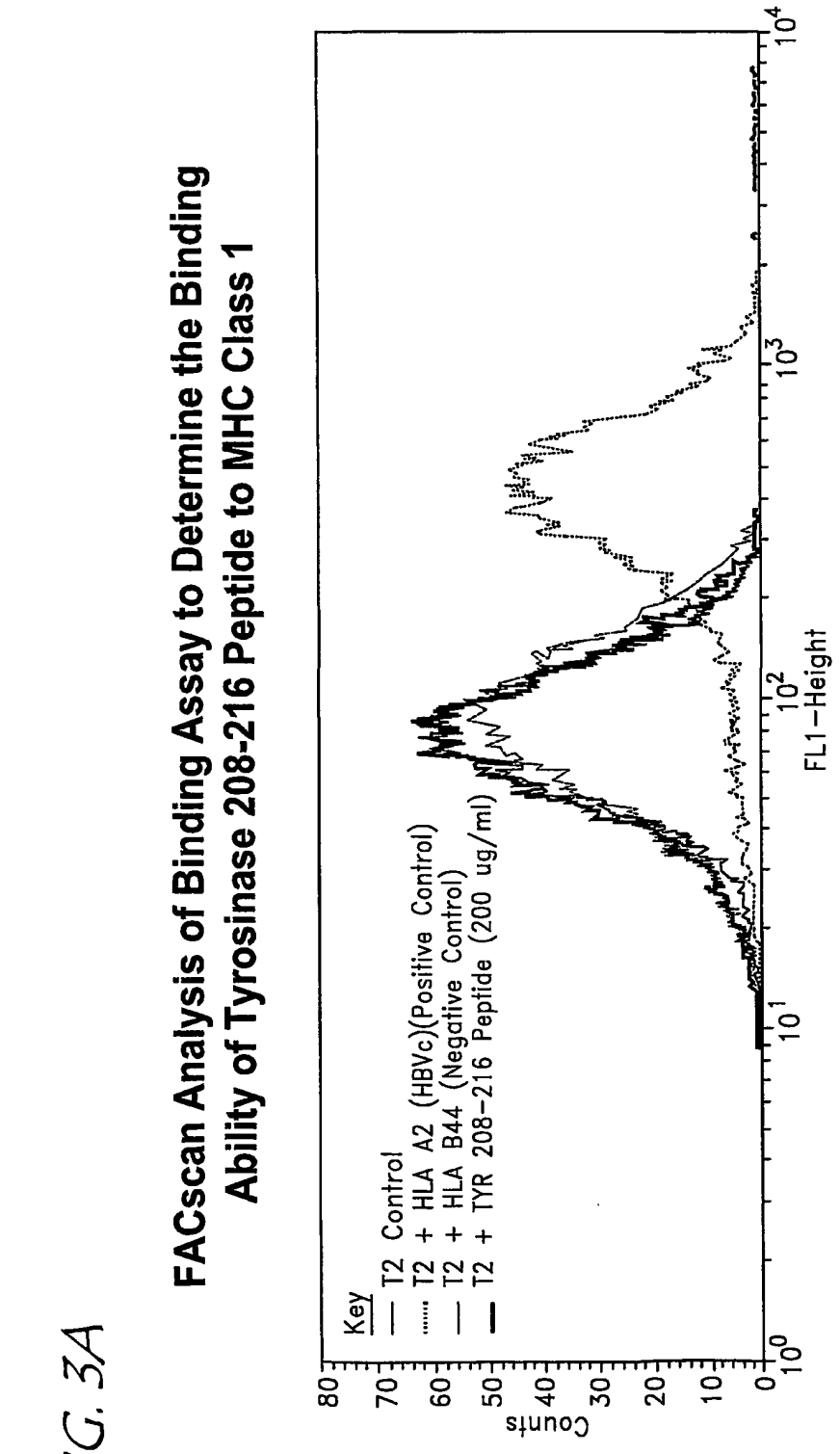

FACscan Analysis of Binding Assay to Determine the Binding Ability of Tyrosinase 208-216 Peptide to MHC Class 1
Key
T2 Control
T2 + HLA A2 (HBVc)(Positive Control)
T2 + HLA B44 (Negative Control)
T2 + TYR 208-216 Peptide (200 ug/ml)
Counts
FL1-Height
F1 (HLA A2 Peptide) = 3.13
F1 (TYR 208-216 Peptide) = 0.01

FIG. 3B

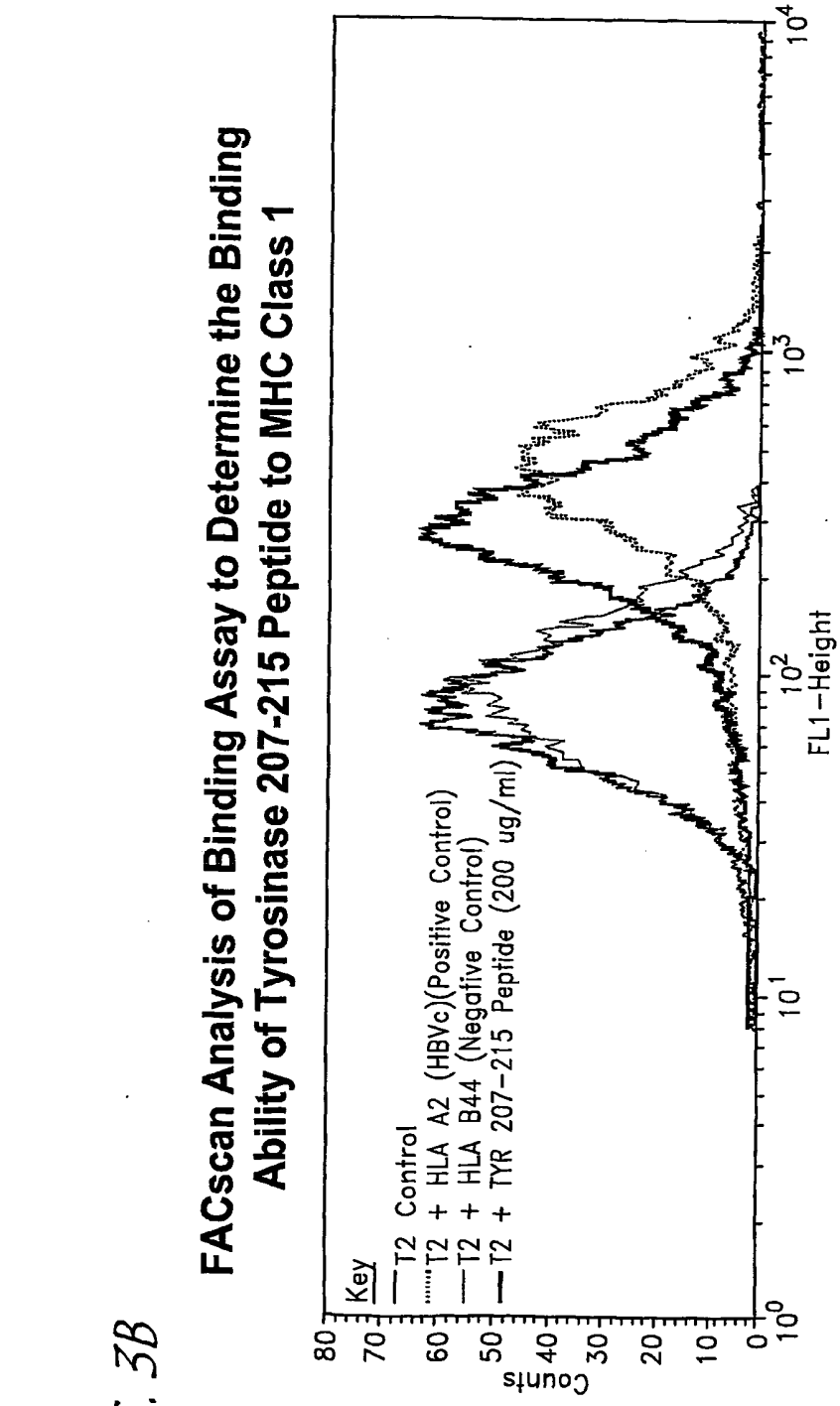
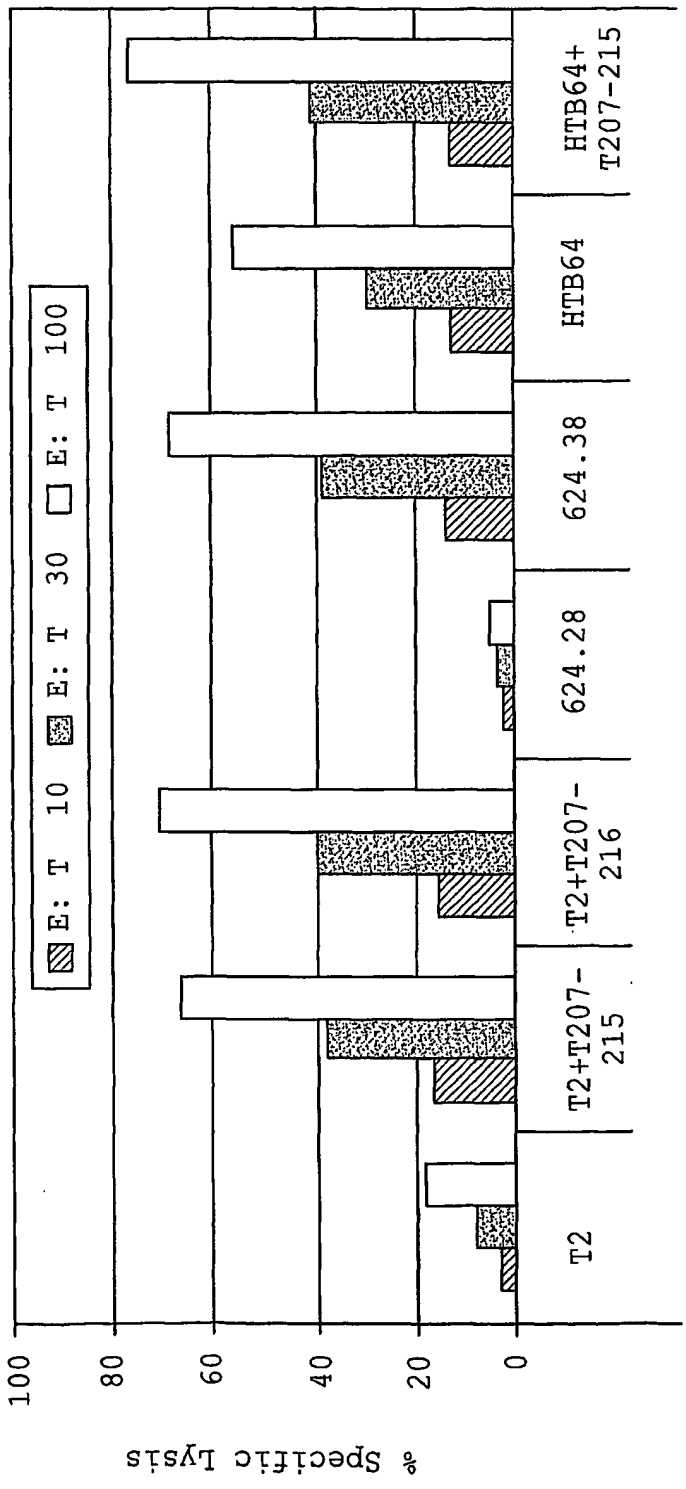

FACscan Analysis of Binding Assay to Determine the Binding Ability of Tyrosinase 207-215 Peptide to MHC Class 1
Key
T2 Control
T2 + HLA A2 (HBVc)(Positive Control)
T2 + HLA B44 (Negative Control)
T2 + TYR 207-215 Peptide (200 ug/ml)
Counts
FL1-Height
F1 (HLA A2 Peptide) = 3.13
F1 (TYR 207-215 Peptide) = 2.00

FIG. 3C


HLA A2 restricted and tyrosinase specific lysis by CTL from Tyr207-215 IVS blood
E: T 10
E: T 30
E: T 100
% Specific Lysis
100
80
60
40
20
0
T2
T2+T207-215
T2+T207-216
624.28
624.38
HTB64
HTB64+ T207-215
CTL from Tyr 207-215 IVS blood

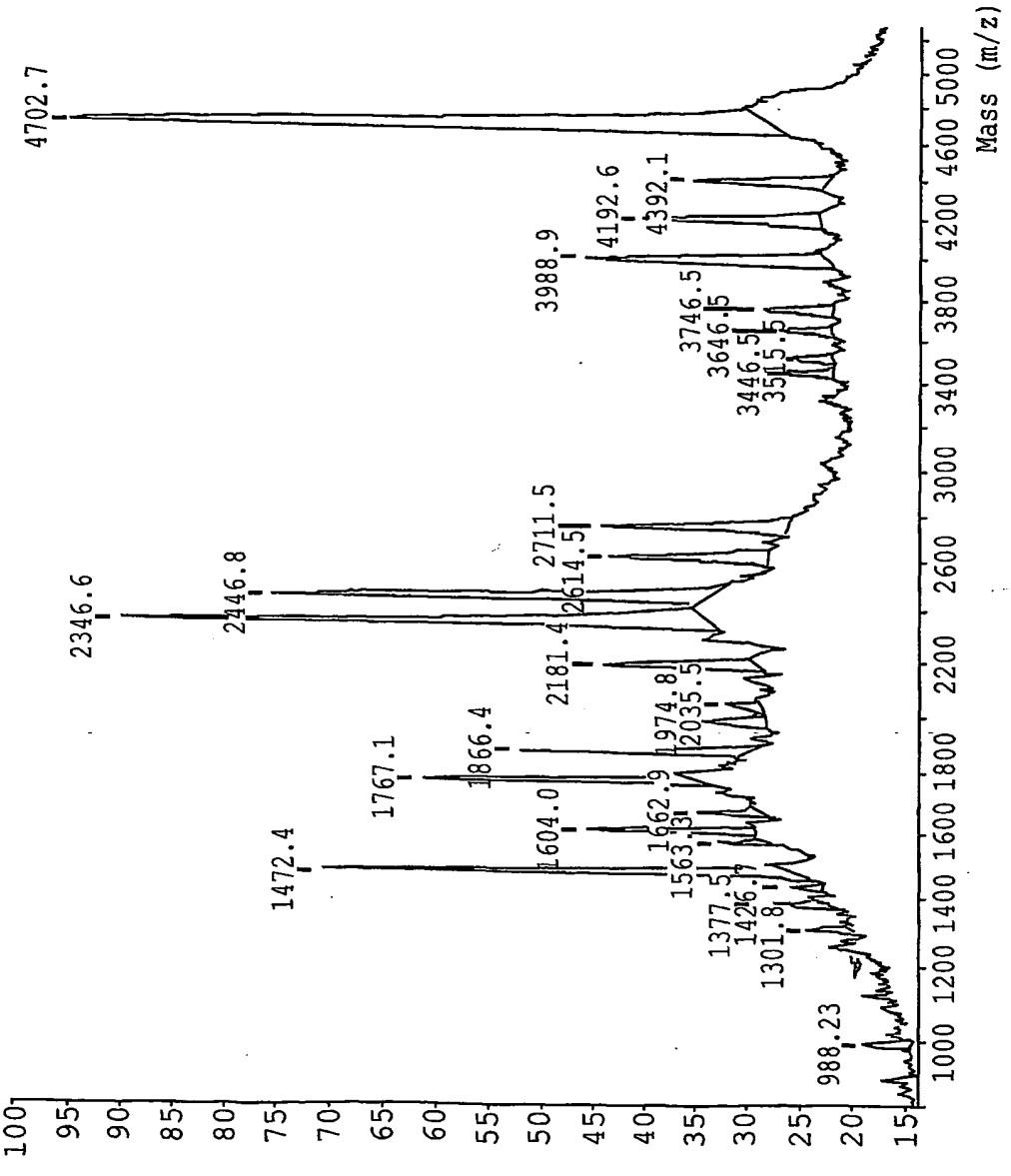

4702.7
2346.6
2446.8
1472.4
1767.1
1866.4
1604.0
1662.9
1563.1
1377.5
1426.7
1301.8
988.23
2711.5
2614.5
2181.4
2035.5
1974.8
3988.9
4192.6
4392.1
3746.5
3646.5
3446.5
Mass (m/z)

FIG. 4

FIG. 5

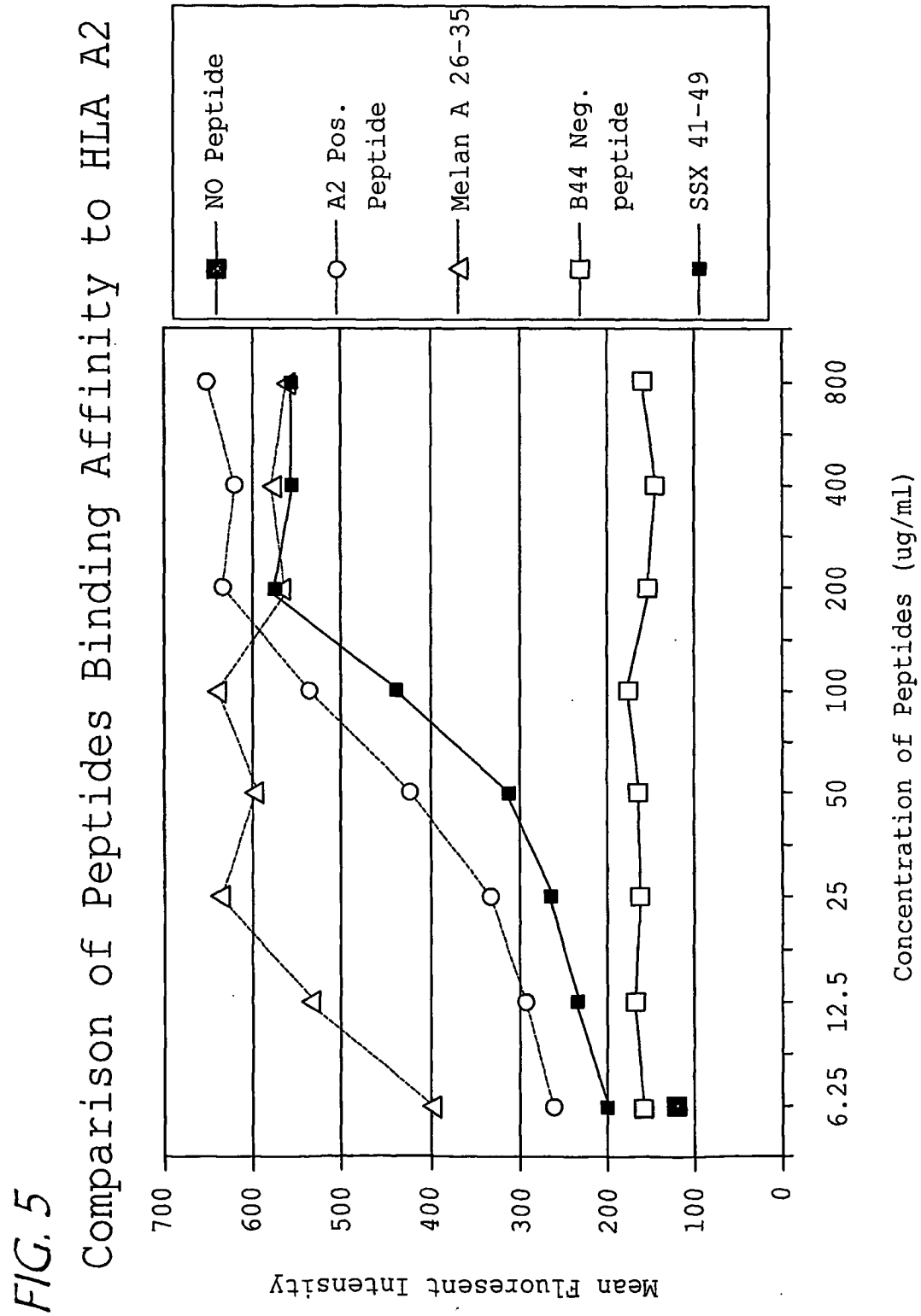

Comparison of Peptides Binding Affinity to HLA A2
NO Peptide
A2 Pos. Peptide
Melan A 26-35
B44 Neg. peptide
SSX 41-49
Mean Fluorescent Intensity
0
100
200
300
400
500
600
700
6.25
12.5
25
50
100
200
400
800
Concentration of Peptides (ug/ml)

FIG. 6

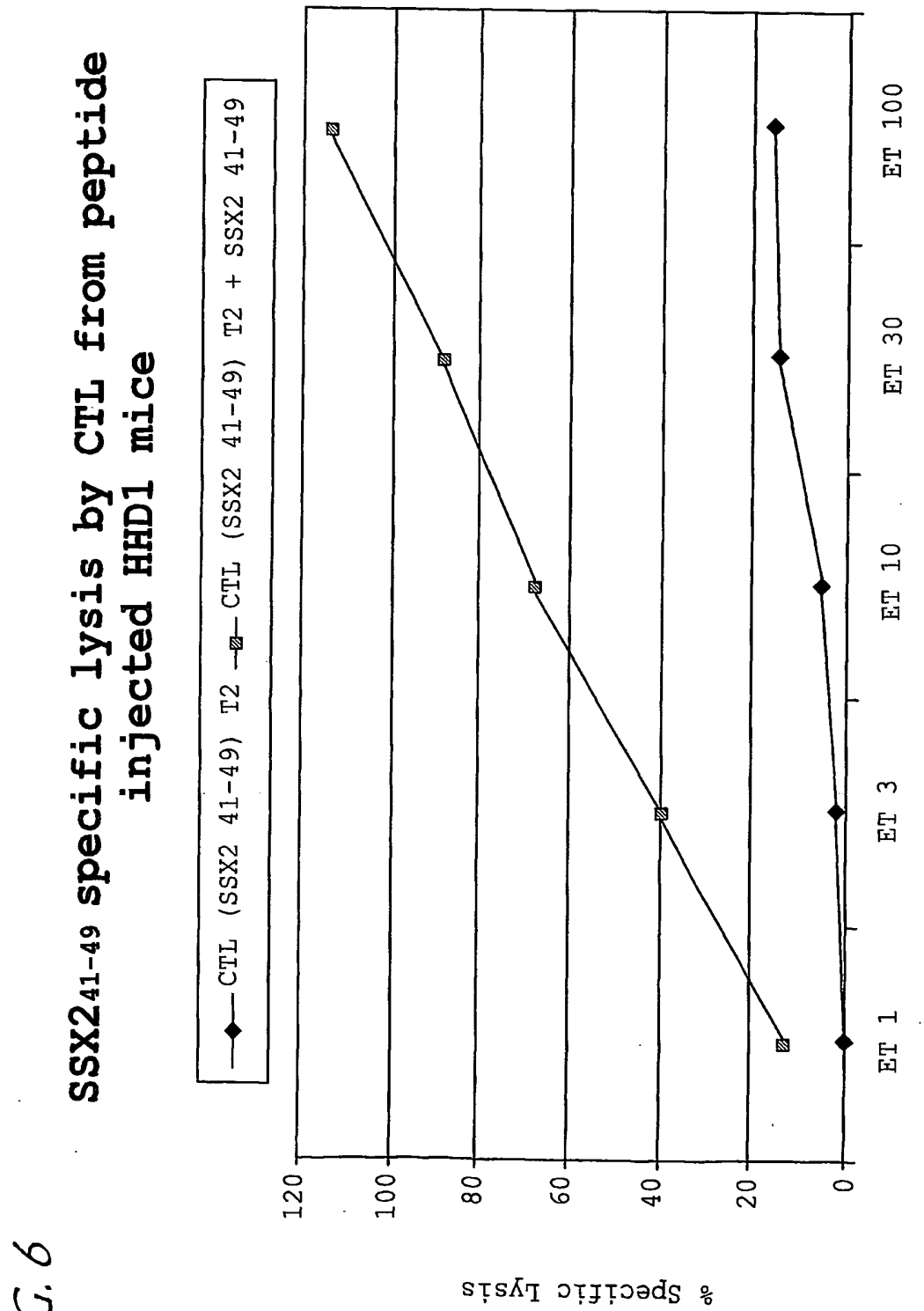
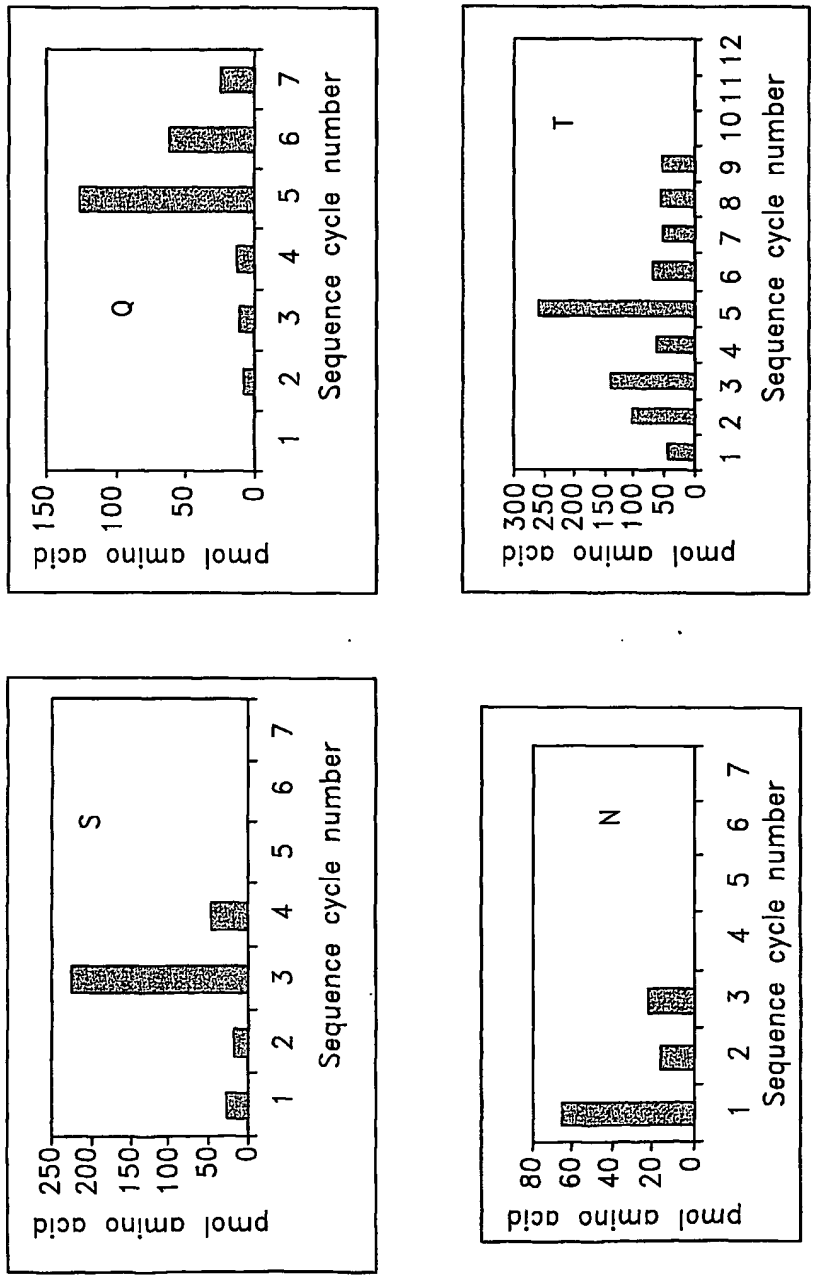

SSX2 41-49 specific lysis by CTL from peptide injected HHD1 mice
CTL (SSX2 41-49) T2
CTL (SSX2 41-49) T2 + SSX2 41-49
% Specific Lysis
120
100
80
60
40
20
0
ET 1
ET 3
ET 10
ET 30
ET 100

FIG. 7A

163-AF**S**P**Q**GMPEGDLVYV**N**YAR**T**EDFFKLERDM-192



Pool sequencing of PSMA_163-192 Digested for 60 min by proteasome

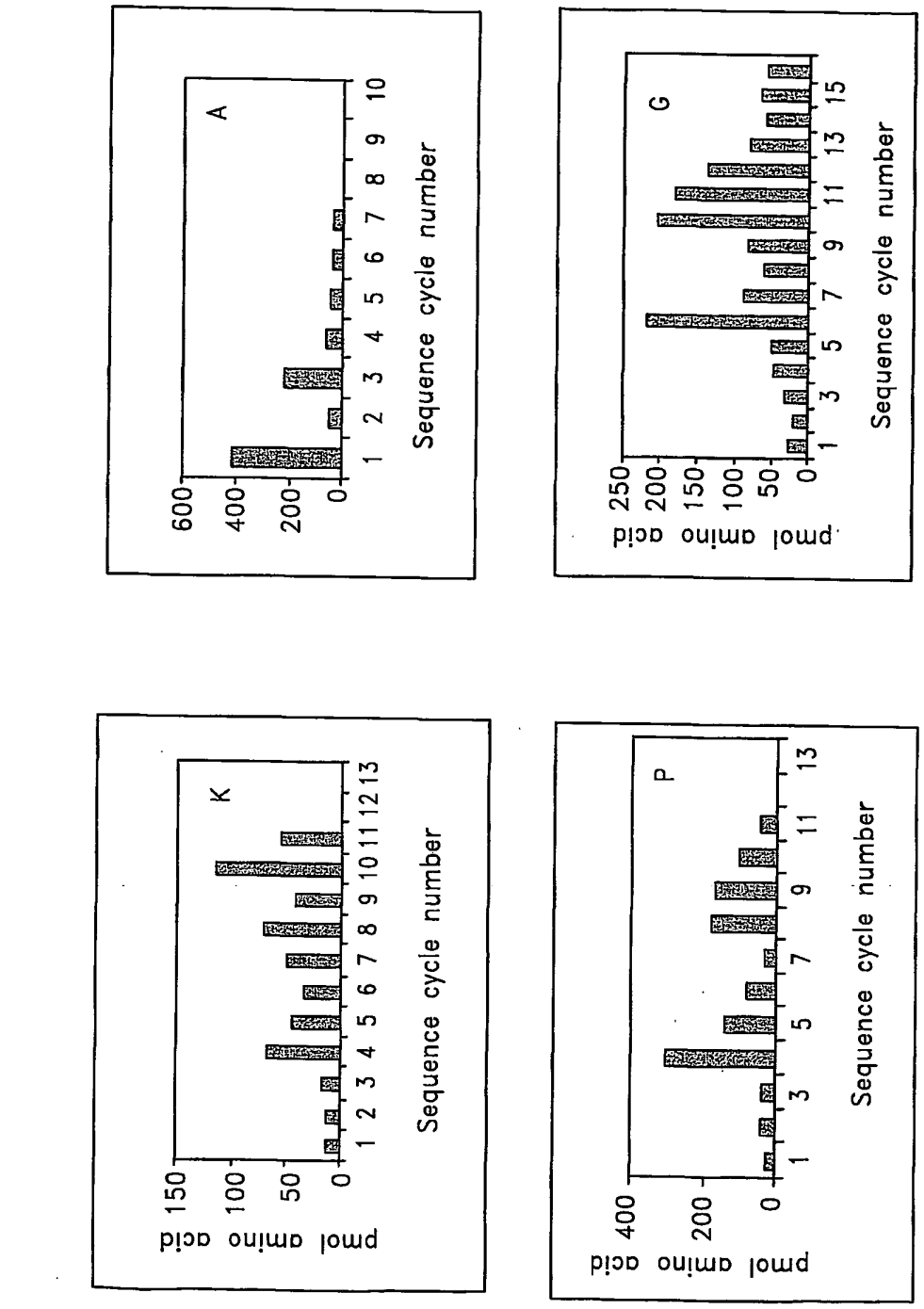
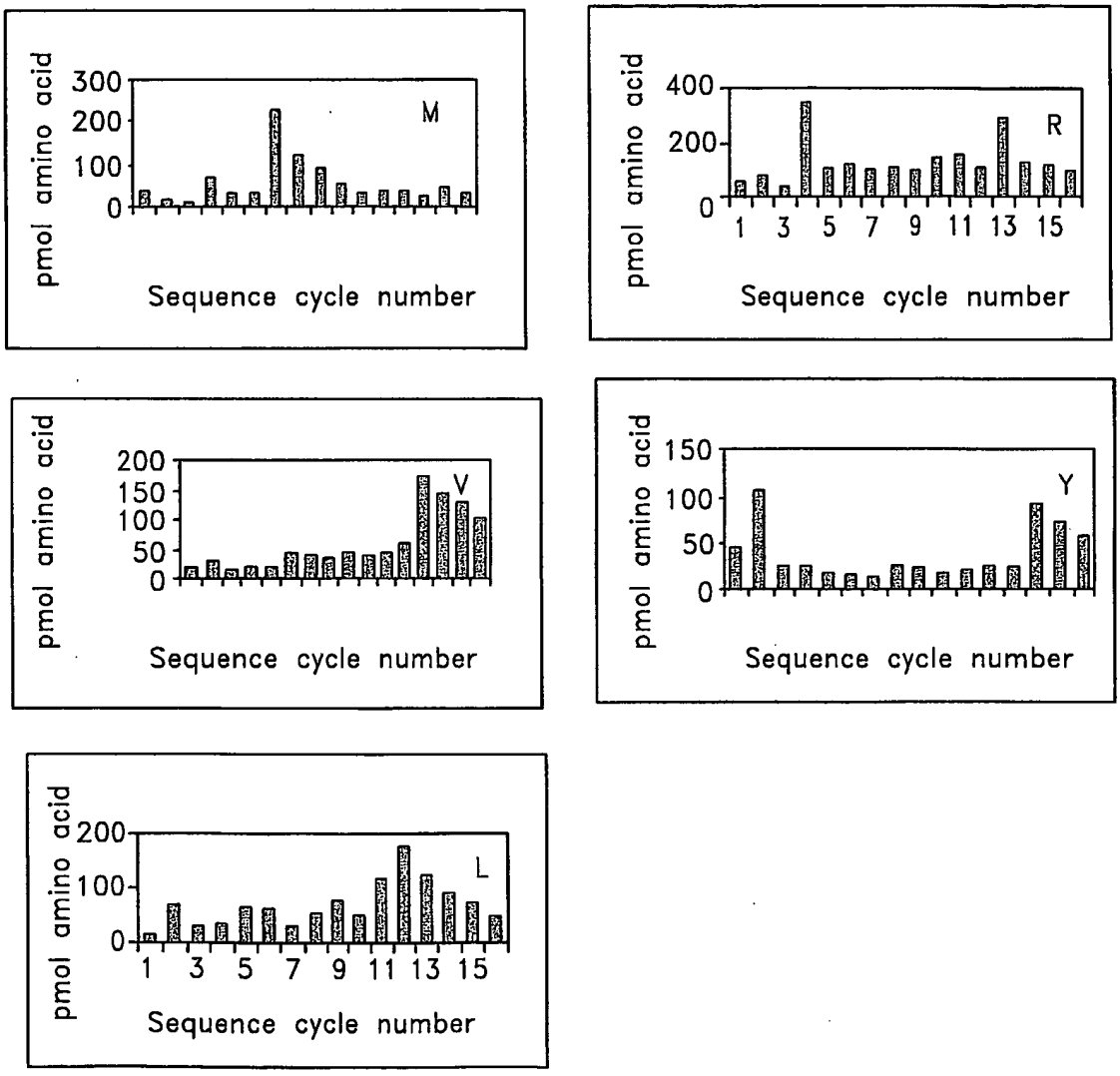


FIG. 7B

Pool sequencing of PSMA_163–192 Digested for 60 min by proteasome



Pool sequencing of PSMA_163–192 Digested for 60 min by proteasome

FIG. 7C

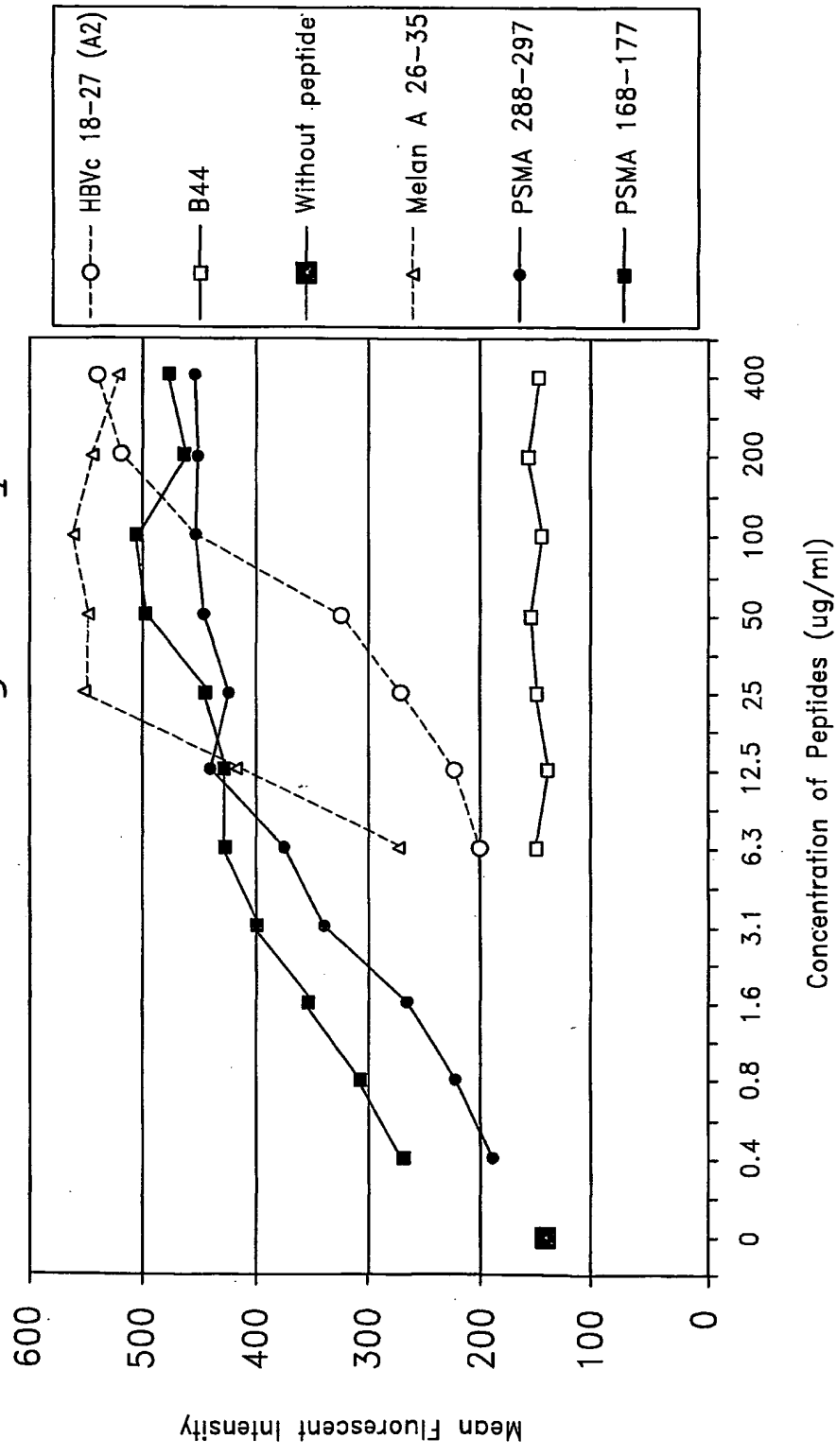
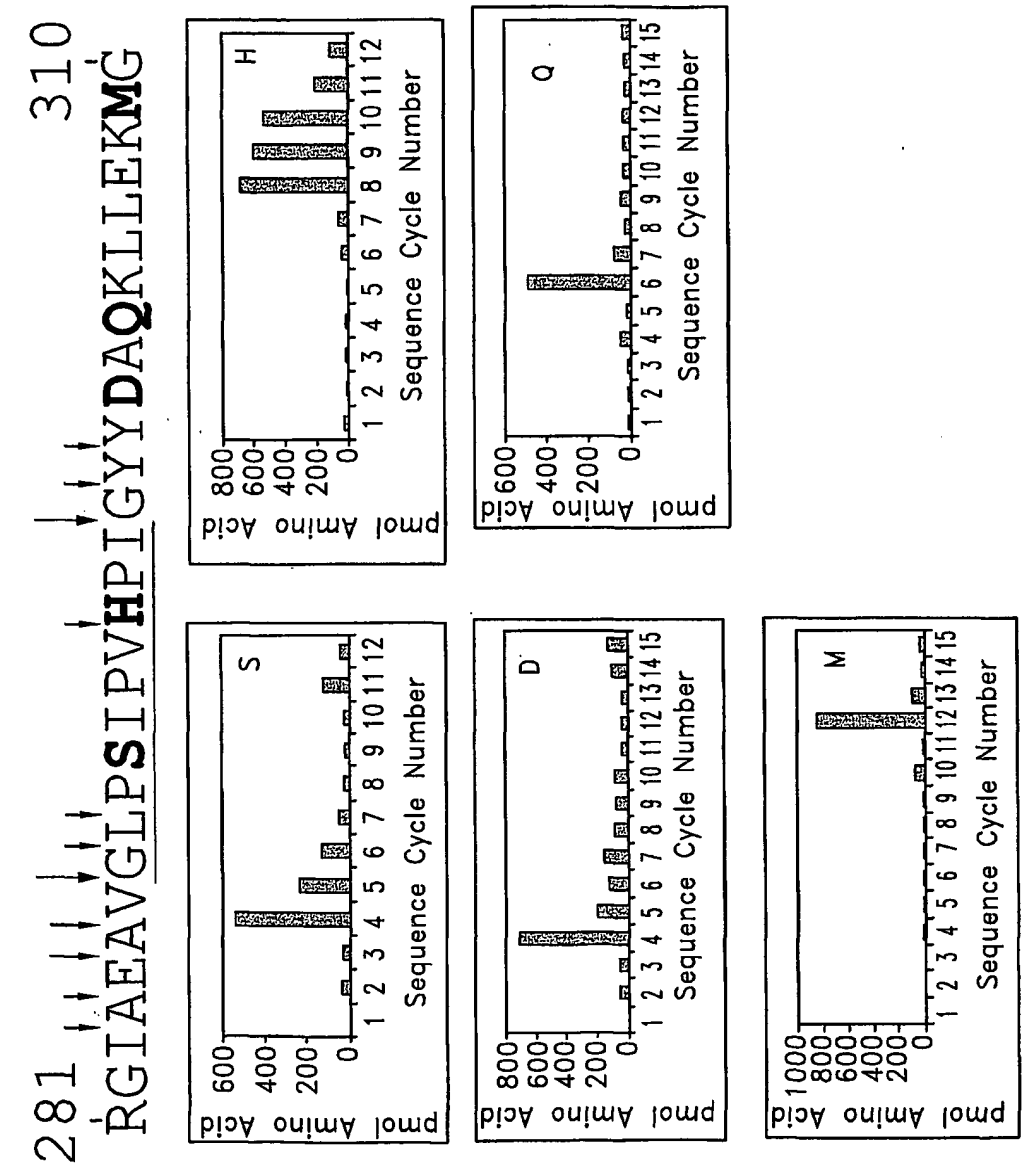

HLA A2 Binding Assay
HBVc 18-27 (A2)
B44
Without peptide
Melan A 26-35
PSMA 288-297
PSMA 168-177
Mean Fluorescent Intensity
600
500
400
300
200
100
0
0
0.4
0.8
1.6
3.1
6.3
12.5
25
50
100
200
400
Concentration of Peptides (ug/ml)

FIG. 8

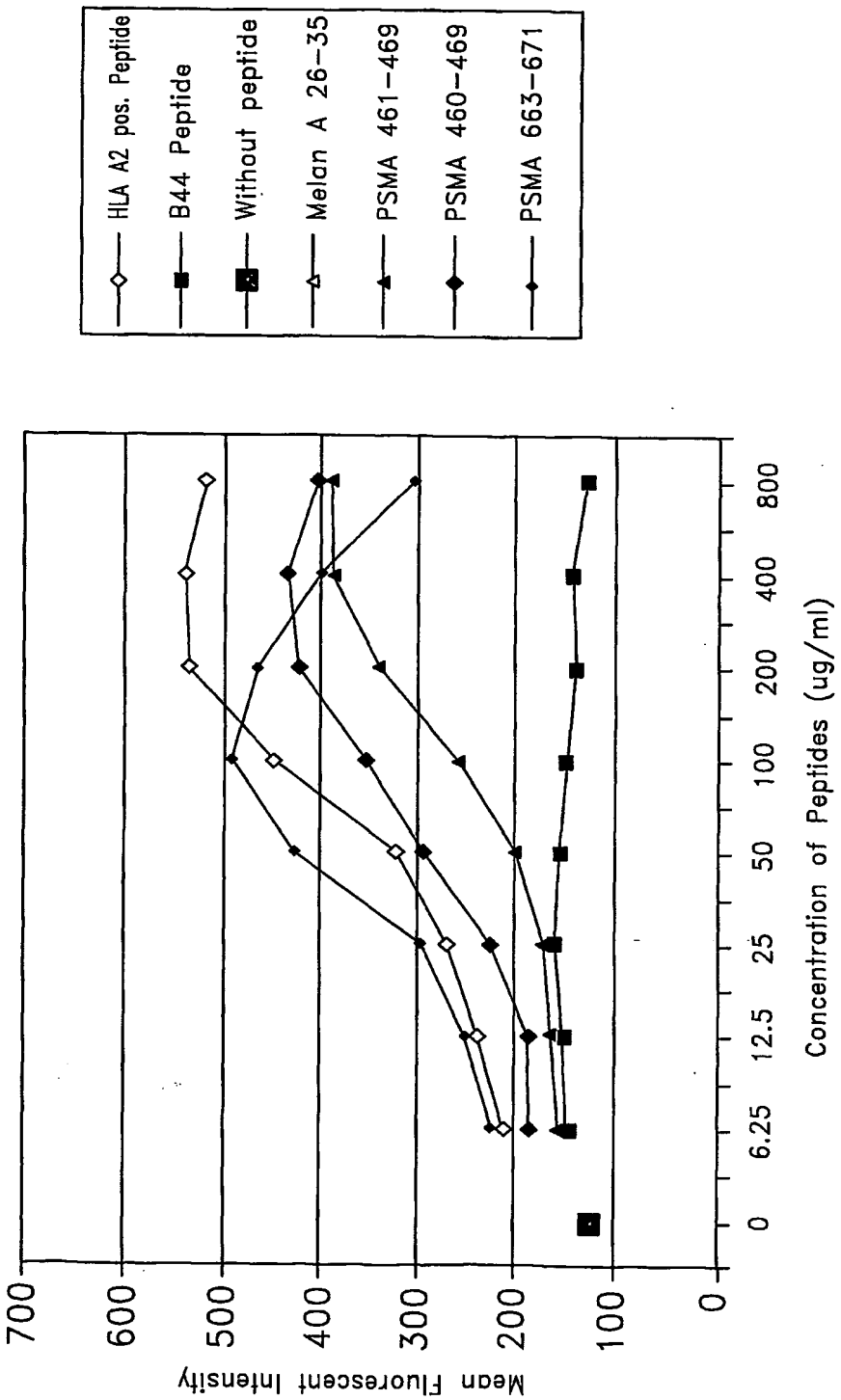
FIG. 9



Pool sequencing of PSMA_281_310 Digested for 60 min by Proteasome

FIG. 10

Comparison of Peptides Binding Affinity to HLA A2 by Binding Assay



Autologous DC Present A1 Peptide to CD8 T cell

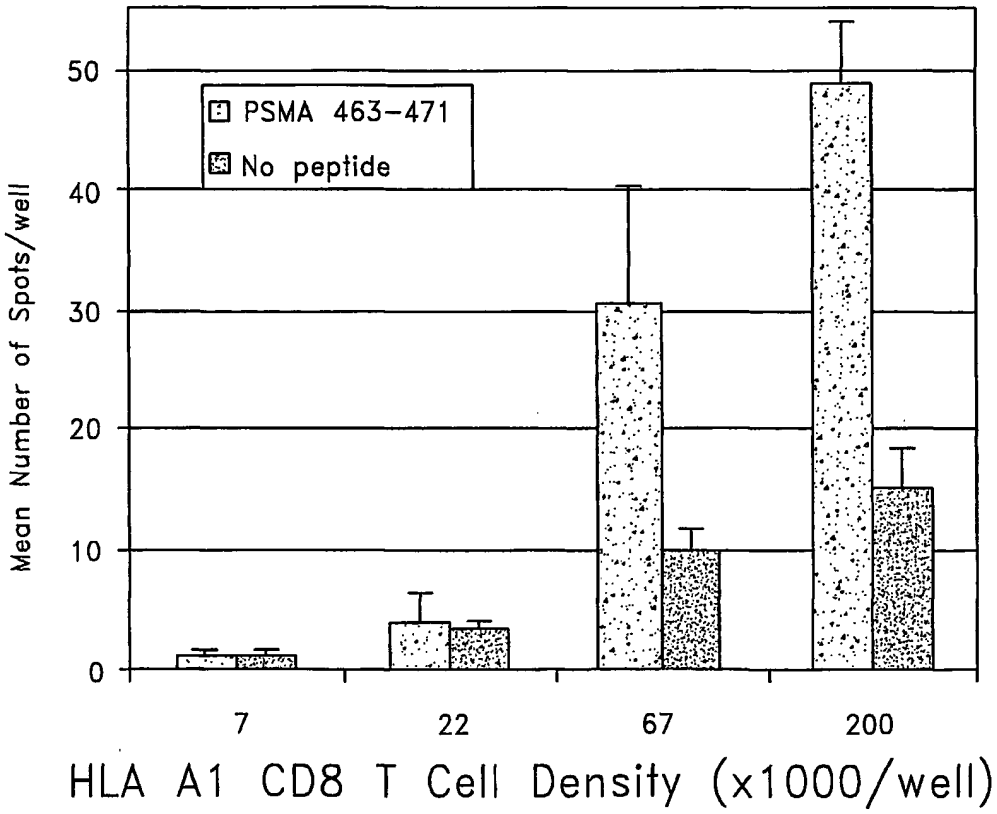


FIG. 11

Secretion of IFNgama Was Blocked by Anti-A1 Antibody

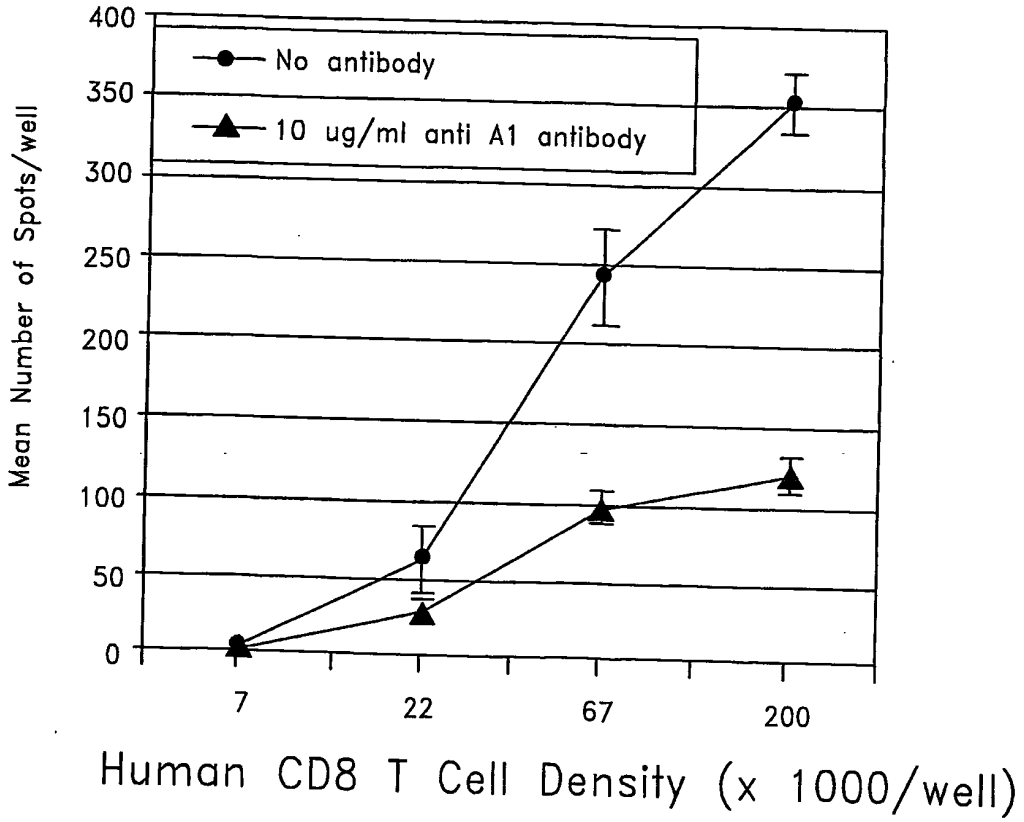


FIG. 12

FIG. 13

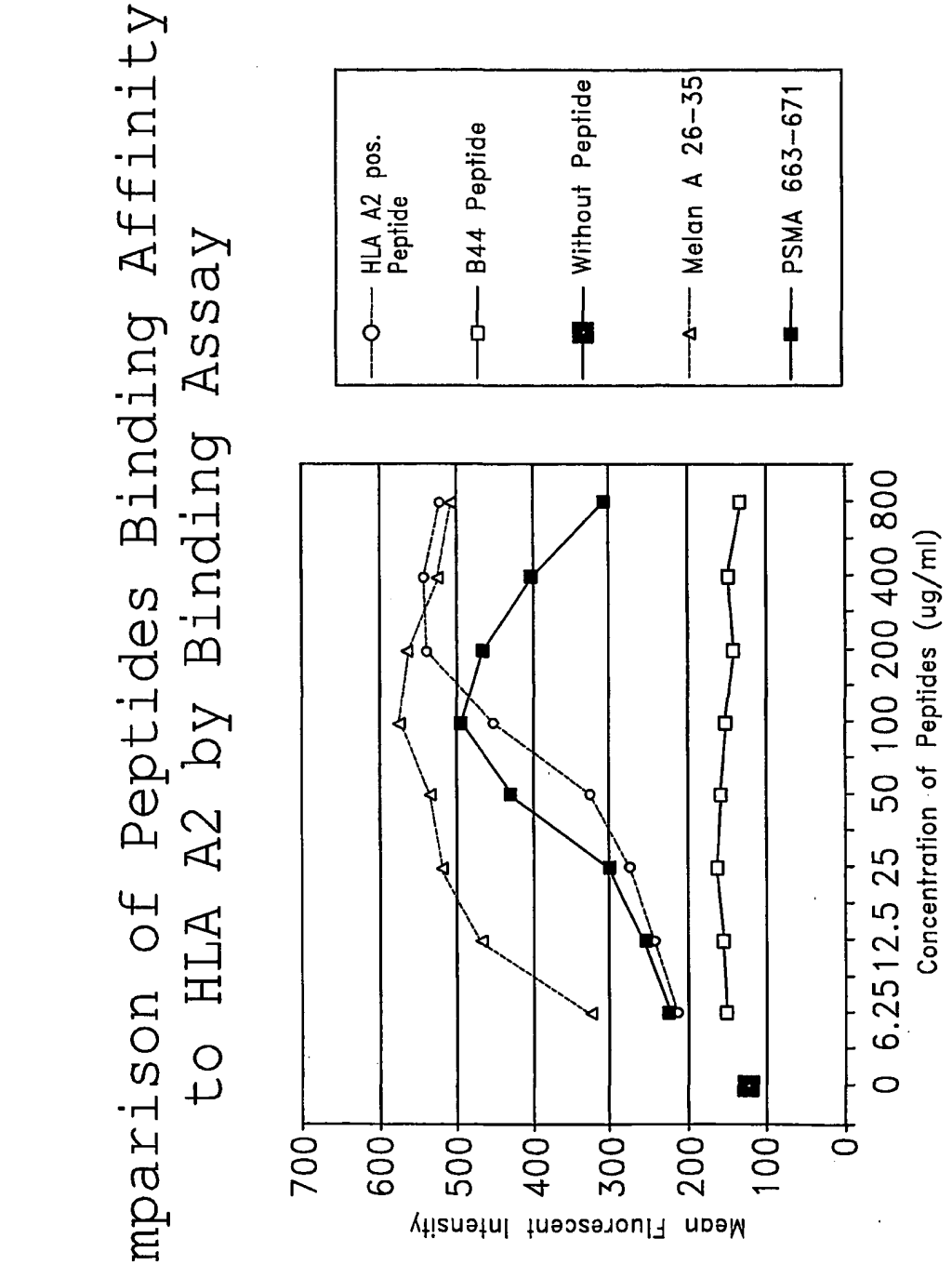
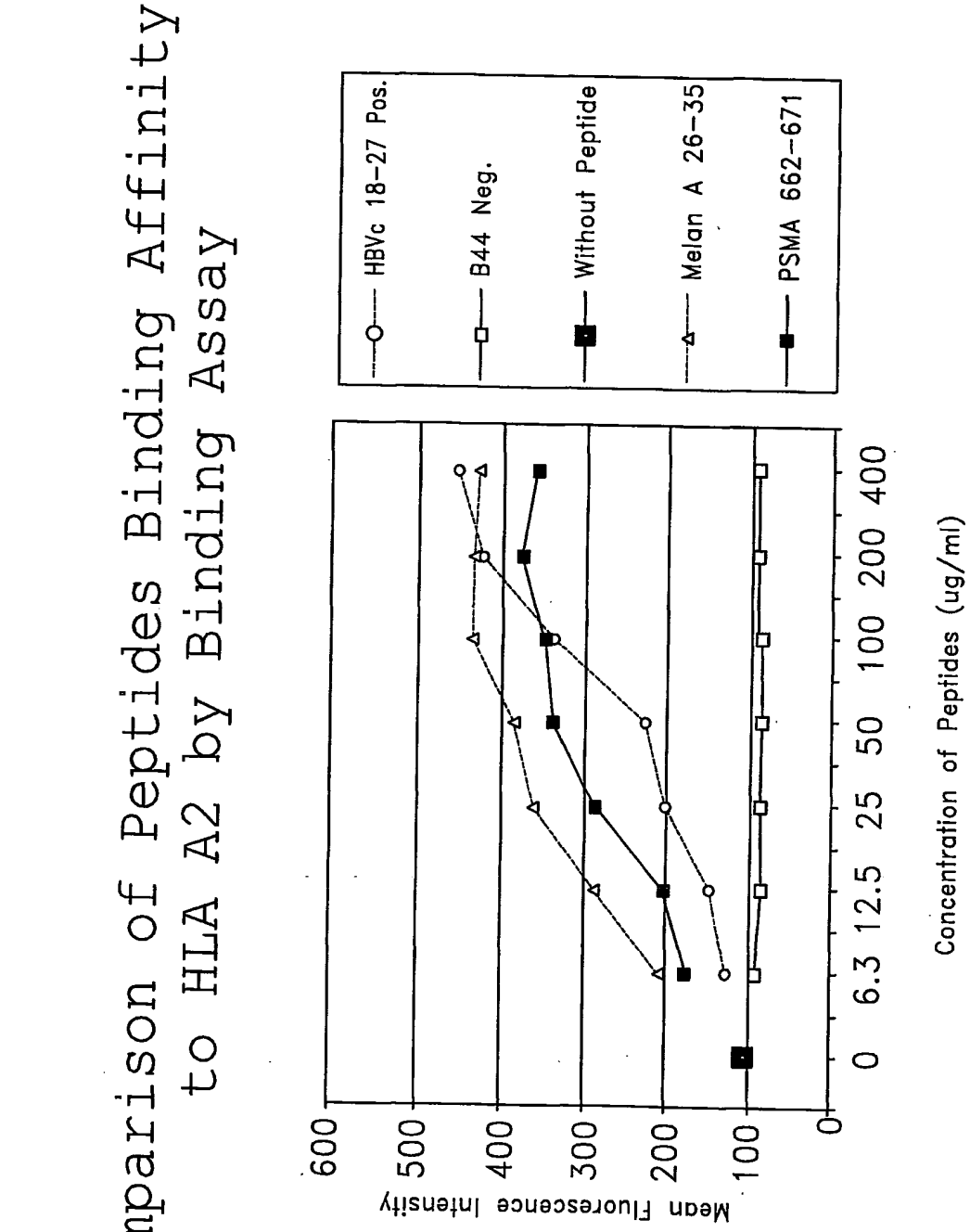

Comparison of Peptides Binding Affinity to HLA A2 by Binding Assay
HLA A2 pos. Peptide
B44 Peptide
Without Peptide
Melan A 26-35
PSMA 663-671
Mean Fluorescent Intensity
700
600
500
400
300
200
100
0
0 6.25 12.5 25 50 100 200 400 800
Concentration of Peptides (ug/ml)

FIG. 14


Comparison of Peptides Binding Affinity to HLA A2 by Binding Assay
HBVc 18-27 Pos.
B44 Neg.
Without Peptide
Melan A 26-35
PSMA 662-671
Mean Fluorescence Intensity
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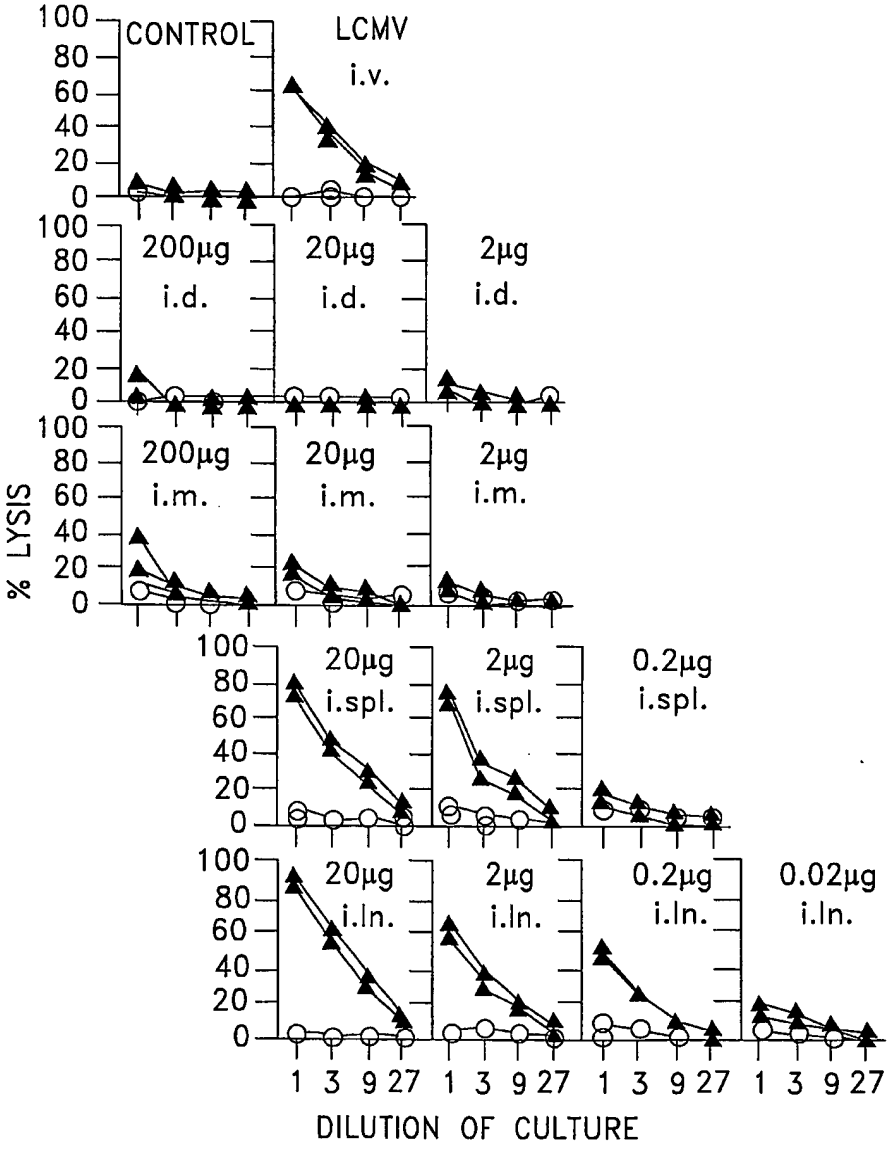
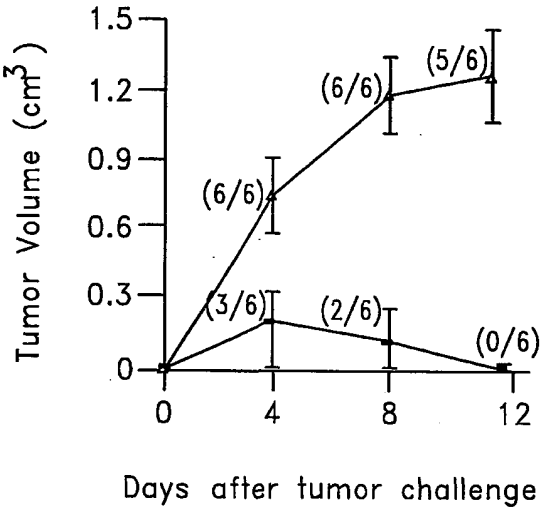
Concentration of Peptides (ug/ml)



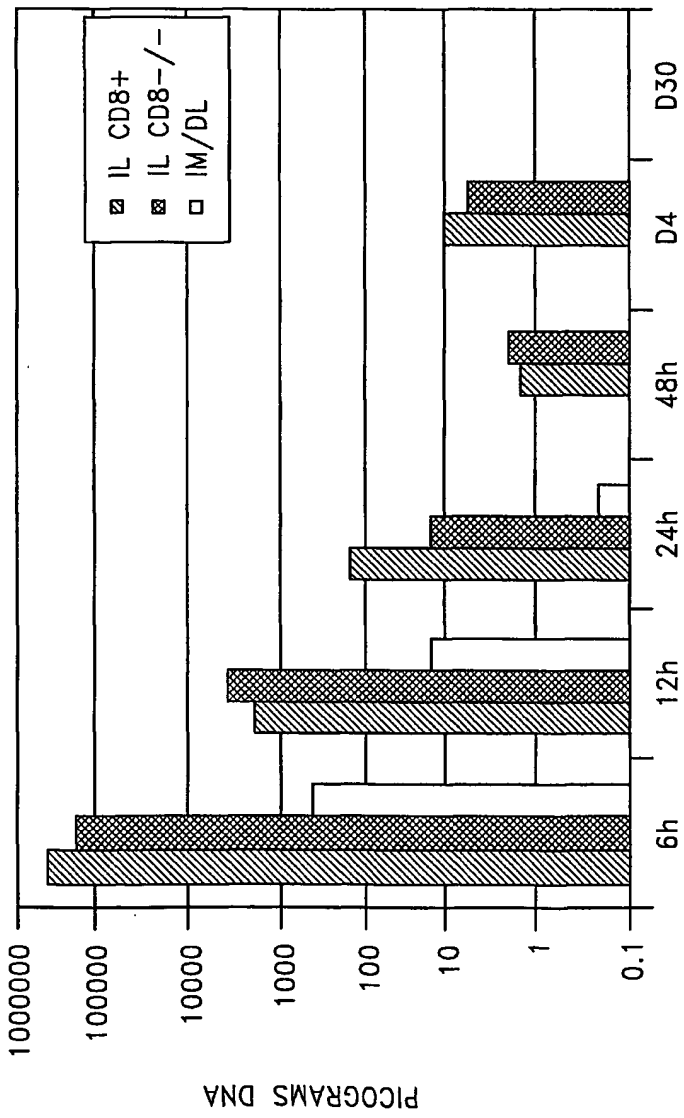
Graphs show lysis of unpulsed EL4 cells (open circles) and EL4 cells pulsed with gp33 peptide (solid triangles). Symbols represent individual mice and one of three similar experiments is shown.

FIG. 15



Mean tumor volumes ± 1SD are shown for mice immunized with pEFGPL33A DNA (solid circles) or control pEGFP-N3 DNA (open triangles). Numbers in brackets indicate number of mice with tumors/total number of mice in group. One of two similar experiments is shown.

FIG. 16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IL CD8-/-
IM/DL
PICOGRAMS DNA
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10000
1000
100
10
1
0.1
6h
12h
24h
48h
D4
D30

FIG. 17

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LIU, Liping
XIE, Zhidong

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35 40 45
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50 55 60
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145                 150                 155                 160
Asn Gly Ser Thr Pro Met Phe Asn Asp Ile Asn Ile Tyr Asp Leu Phe
                165                 170                 175
Val Trp Met His Tyr Tyr Val Ser Met Asp Ala Leu Leu Gly Gly Ser
            180                 185                 190
Glu Ile Trp Arg Asp Ile Asp Phe Ala His Glu Ala Pro Ala Phe Leu
        195                 200                 205
Pro Trp His Arg Leu Phe Leu Leu Arg Trp Glu Gln Glu Ile Gln Lys
    210                 215                 220
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225                 230                 235                 240
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    290                 295                 300
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                325                 330                 335
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            340                 345                 350
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    370                 375                 380
Ile Phe Leu Leu His His Ala Phe Val Asp Ser Ile Phe Glu Gln Trp
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Tyr Arg Asn Gly Asp Phe Phe Ile Ser Ser Lys Asp Leu Gly Tyr Asp
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Tyr Ser Tyr Leu Gln Asp Ser Asp Pro Asp Ser Phe Gln Asp Tyr Ile
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Ser Leu Leu Cys Arg His Lys Arg Lys Gln Leu Pro Glu Glu Lys Gln
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Val Tyr Met Lys Arg Lys Tyr Glu Ala Met Thr Lys Leu Gly Phe Lys
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Ala Thr Leu Pro Pro Phe Met Cys Asn Lys Arg Ala Glu Asp Phe Gln
65 70 75 80
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Pro His Leu Ala Gly Thr Glu Gln Asn Phe Gln Leu Ala Lys Gln Ile
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Gln Ser Gln Trp Lys Glu Phe Gly Leu Asp Ser Val Glu Leu Ala His
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            180                 185                 190
Lys Ile Asn Cys Ser Gly Lys Ile Val Ile Ala Arg Tyr Gly Lys Val
        195                 200                 205
Phe Arg Gly Asn Lys Val Lys Asn Ala Gln Leu Ala Gly Ala Lys Gly
    210                 215                 220
Val Ile Leu Tyr Ser Asp Pro Ala Asp Tyr Phe Ala Pro Gly Val Lys
225                 230                 235                 240
Ser Tyr Pro Asp Gly Trp Asn Leu Pro Gly Gly Gly Val Gln Arg Gly
                245                 250                 255
Asn Ile Leu Asn Leu Asn Gly Ala Gly Asp Pro Leu Thr Pro Gly Tyr
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305                 310                 315                 320
Gly Ser Leu Lys Val Pro Tyr Asn Val Gly Pro Gly Phe Thr Gly Asn
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Phe Ser Thr Gln Lys Val Lys Met His Ile His Ser Thr Asn Glu Val
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        355                 360                 365
Asp Arg Tyr Val Ile Leu Gly Gly His Arg Asp Ser Trp Val Phe Gly
    370                 375                 380
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Ser Phe Gly Thr Leu Lys Lys Glu Gly Trp Arg Pro Arg Arg Thr Ile
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            660                 665                 670
Arg Ala Phe Ile Asp Pro Leu Gly Leu Pro Asp Arg Pro Phe Tyr Arg
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His Val Ile Tyr Ala Pro Ser Ser His Asn Lys Tyr Ala Gly Glu Ser
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Phe Leu Pro Trp His Arg Leu Phe Leu
1 5

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Leu Pro Trp His Arg Leu Phe Leu Leu
1 5

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Tyr Phe Ser Lys Glu Glu Trp Glu Lys Met Lys Ala Ser Glu Lys Ile
1 5 10 15
Phe Tyr Val Tyr Met Lys Arg Lys Tyr Glu Ala Met Thr Lys Leu Gly
20 25 30
Phe Lys Ala Thr Leu Pro
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<400> 11

Phe Ser Lys Glu Glu Trp Glu Lys Met
1 5

<210> 12
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Lys Met Lys Ala Ser Glu Lys Ile Phe
1 5

<210> 13
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<400> 13
Met Lys Ala Ser Glu Lys Ile Phe Tyr
1 5

<210> 14
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<400> 14
Lys Met Lys Ala Ser Glu Lys Ile Phe Tyr
1 5 10

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Lys Ala Ser Glu Lys Ile Phe Tyr Val
1 5

<210> 16
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<400> 16
Met Lys Ala Ser Glu Lys Ile Phe Tyr Val
1 5 10

<210> 17
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Lys Ala Ser Glu Lys Ile Phe Tyr Val Tyr
1 5 10

<210> 18
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<400> 18
Ala Ser Glu Lys Ile Phe Tyr Val Tyr
1 5

<210> 19
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<400> 19
Arg Lys Tyr Glu Ala Met Thr Lys Leu
1 5

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<400> 20
Lys Arg Lys Tyr Glu Ala Met Thr Lys Leu
1 5 10

<210> 21
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<400> 21
Lys Tyr Glu Ala Met Thr Lys Leu Gly Phe
1 5 10

<210> 22
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<400> 22
Tyr Glu Ala Met Thr Lys Leu Gly Phe
1 5

<210> 23
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<400> 23
Glu Ala Met Thr Lys Leu Gly Phe
1 5

<210> 24
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<400> 24
Phe Leu Pro Ser Asp Tyr Phe Pro Ser Val
1 5 10

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Ala Glu Met Gly Lys Tyr Ser Phe Tyr
1 5

<210> 26
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<400> 26
Lys Tyr Ser Glu Lys Ile Ser Tyr Val
1 5

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<400> 27
Lys Val Ser Glu Lys Ile Val Tyr Val
1 5

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<400> 28
Lys Ser Ser Glu Lys Ile Val Tyr Val

1 5

<210> 29
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<400> 29
Lys Ala Ser Glu Lys Ile Ile Tyr Val
1 5

<210> 30
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Ala Phe Ser Pro Gln Gly Met Pro Glu Gly Asp Leu Val Tyr Val Asn
1 5 10 15
Tyr Ala Arg Thr Glu Asp Phe Phe Lys Leu Glu Arg Asp Met
20 25 30

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<400> 31
Gly Met Pro Glu Gly Asp Leu Val Tyr Val Asn Tyr Ala Arg Thr Glu
1 5 10 15
Asp Phe Phe Lys Leu Glu Arg
20

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<400> 32
Met Pro Glu Gly Asp Leu Val Tyr Val
1 5

<210> 33
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<400> 33
Gly Met Pro Glu Gly Asp Leu Val Tyr Val
1 5 10

<210> 34
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<400> 34
Gly Met Pro Glu Gly Asp Leu Val Tyr
1 5

<210> 35
<211> 10
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<400> 35
Gln Gly Met Pro Glu Gly Asp Leu Val Tyr
1 5 10

<210> 36
<211> 8
<212> PRT
<213> Homo sapiens

<400> 36
Met Pro Glu Gly Asp Leu Val Tyr
1 5

<210> 37
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<400> 37
Glu Gly Asp Leu Val Tyr Val Asn Tyr
1 5

<210> 38
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<400> 38
Pro Glu Gly Asp Leu Val Tyr Val Asn Tyr
1 5 10

<210> 39
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<400> 39
Leu Val Tyr Val Asn Tyr Ala Arg Thr Glu

1 5 10

<210> 40
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<400> 40
Val Asn Tyr Ala Arg Thr Glu Asp Phe
1 5

<210> 41
<211> 10
<212> PRT
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<400> 41
Tyr Val Asn Tyr Ala Arg Thr Glu Asp Phe
1 5 10

<210> 42
<211> 9
<212> PRT
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<400> 42
Asn Tyr Ala Arg Thr Glu Asp Phe Phe
1 5

<210> 43
<211> 8
<212> PRT
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<400> 43
Tyr Ala Arg Thr Glu Asp Phe Phe
1 5

<210> 44
<211> 9
<212> PRT
<213> Homo sapiens

<400> 44
Arg Thr Glu Asp Phe Phe Lys Leu Glu
1 5

<210> 45
<211> 30
<212> PRT
<213> Homo sapiens

<400> 45
Arg Gly Ile Ala Glu Ala Val Gly Leu Pro Ser Ile Pro Val His Pro
1 5 10 15
Ile Gly Tyr Tyr Asp Ala Gln Lys Leu Leu Glu Lys Met Gly
20 25 30

<210> 46
<211> 25
<212> PRT
<213> Homo sapiens

<400> 46
Ile Ala Glu Ala Val Gly Leu Pro Ser Ile Pro Val His Pro Ile Gly
1 5 10 15
Tyr Tyr Asp Ala Gln Lys Leu Leu Glu
20 25

<210> 47
<211> 9
<212> PRT
<213> Homo sapiens

<400> 47
Leu Pro Ser Ile Pro Val His Pro Ile
1 5

<210> 48
<211> 10
<212> PRT
<213> Homo sapiens

<400> 48
Gly Leu Pro Ser Ile Pro Val His Pro Ile
1 5 10

<210> 49
<211> 9
<212> PRT
<213> Homo sapiens

<400> 49
Ile Gly Tyr Tyr Asp Ala Gln Lys Leu
1 5

<210> 50
<211> 10
<212> PRT
<213> Homo sapiens

<400> 50
Pro Ile Gly Tyr Tyr Asp Ala Gln Lys Leu

1 5 10

<210> 51
<211> 9
<212> PRT
<213> Homo sapiens

<400> 51
Ser Ile Pro Val His Pro Ile Gly Tyr
1 5

<210> 52
<211> 10
<212> PRT
<213> Homo sapiens

<400> 52
Pro Ser Ile Pro Val His Pro Ile Gly Tyr
1 5 10

<210> 53
<211> 8
<212> PRT
<213> Homo sapiens

<400> 53
Ile Pro Val His Pro Ile Gly Tyr
1 5

<210> 54
<211> 9
<212> PRT
<213> Homo sapiens

<400> 54
Tyr Tyr Asp Ala Gln Lys Leu Leu Glu
1 5

<210> 55
<211> 27
<212> PRT
<213> Homo sapiens

<400> 55
Ser Ser Ile Glu Gly Asn Tyr Thr Leu Arg Val Asp Cys Thr Pro Leu
1 5 10 15
Met Tyr Ser Leu Val His Leu Thr Lys Glu Leu
20 25

<210> 56
<211> 9

<212> PRT
<213> Homo sapiens

<400> 56
Ile Glu Gly Asn Tyr Thr Leu Arg Val
1 5

<210> 57
<211> 10
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<400> 57
Ser Ile Glu Gly Asn Tyr Thr Leu Arg Val
1 5 10

<210> 58
<211> 8
<212> PRT
<213> Homo sapiens

<400> 58
Glu Gly Asn Tyr Thr Leu Arg Val
1 5

<210> 59
<211> 9
<212> PRT
<213> Homo sapiens

<400> 59
Thr Leu Arg Val Asp Cys Thr Pro Leu
1 5

<210> 60
<211> 10
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<400> 60
Tyr Thr Leu Arg Val Asp Cys Thr Pro Leu
1 5 10

<210> 61
<211> 9
<212> PRT
<213> Homo sapiens

<400> 61
Leu Arg Val Asp Cys Thr Pro Leu Met
1 5

<210> 62
<211> 9
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<400> 62
Arg Val Asp Cys Thr Pro Leu Met Tyr
1 5

<210> 63
<211> 10
<212> PRT
<213> Homo sapiens

<400> 63
Leu Arg Val Asp Cys Thr Pro Leu Met Tyr
1 5 10

<210> 64
<211> 35
<212> PRT
<213> Homo sapiens

<400> 64
Phe Asp Lys Ser Asn Pro Ile Val Leu Arg Met Met Asn Asp Gln Leu
1 5 10 15
Met Phe Leu Glu Arg Ala Phe Ile Asp Pro Leu Gly Leu Pro Asp Arg
20 25 30
Pro Phe Tyr
35

<210> 65
<211> 22
<212> PRT
<213> Homo sapiens

<400> 65
Val Leu Arg Met Met Asn Asp Gln Leu Met Phe Leu Glu Arg Ala Phe
1 5 10 15
Ile Asp Pro Leu Gly Leu
20

<210> 66
<211> 9
<212> PRT
<213> Homo sapiens

<400> 66
Met Met Asn Asp Gln Leu Met Phe Leu
1 5

<210> 67
<211> 10
<212> PRT
<213> Homo sapiens

<400> 67
Arg Met Met Asn Asp Gln Leu Met Phe Leu
1 5 10

<210> 68
<211> 9
<212> PRT
<213> Homo sapiens

<400> 68
Arg Met Met Asn Asp Gln Leu Met Phe
1 5

<210> 69
<211> 17
<212> PRT
<213> Homo sapiens

<400> 69
Met Leu Leu Ala Val Leu Tyr Cys Leu Leu Trp Ser Phe Gln Thr Ser
1 5 10 15
Ala

<210> 70
<211> 661
<212> PRT
<213> Homo sapiens

<400> 70
Met Asp Leu Val Leu Lys Arg Cys Leu Leu His Leu Ala Val Ile Gly
1 5 10 15
Ala Leu Leu Ala Val Gly Ala Thr Lys Val Pro Arg Asn Gln Asp Trp
20 25 30
Leu Gly Val Ser Arg Gln Leu Arg Thr Lys Ala Trp Asn Arg Gln Leu
35 40 45
Tyr Pro Glu Trp Thr Glu Ala Gln Arg Leu Asp Cys Trp Arg Gly Gly
50 55 60
Gln Val Ser Leu Lys Val Ser Asn Asp Gly Pro Thr Leu Ile Gly Ala
65 70 75 80
Asn Ala Ser Phe Ser Ile Ala Leu Asn Phe Pro Gly Ser Gln Lys Val
85 90 95
Leu Pro Asp Gly Gln Val Ile Trp Val Asn Asn Thr Ile Ile Asn Gly
100 105 110
Ser Gln Val Trp Gly Gly Gln Pro Val Tyr Pro Gln Glu Thr Asp Asp
115 120 125
Ala Cys Ile Phe Pro Asp Gly Gly Pro Cys Pro Ser Gly Ser Trp Ser
130 135 140
Gln Lys Arg Ser Phe Val Tyr Val Trp Lys Thr Trp Gly Gln Tyr Trp

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145                 150                 155                 160
Gln Val Leu Gly Gly Pro Val Ser Gly Leu Ser Ile Gly Thr Gly Arg
                165                 170                 175
Ala Met Leu Gly Thr His Thr Met Glu Val Thr Val Tyr His Arg Arg
            180                 185                 190
Gly Ser Arg Ser Tyr Val Pro Leu Ala His Ser Ser Ser Ala Phe Thr
        195                 200                 205
Ile Thr Asp Gln Val Pro Phe Ser Val Ser Val Ser Gln Leu Arg Ala
    210                 215                 220
Leu Asp Gly Gly Asn Lys His Phe Leu Arg Asn Gln Pro Leu Thr Phe
225                 230                 235                 240
Ala Leu Gln Leu His Asp Pro Ser Gly Tyr Leu Ala Glu Ala Asp Leu
                245                 250                 255
Ser Tyr Thr Trp Asp Phe Gly Asp Ser Ser Gly Thr Leu Ile Ser Arg
            260                 265                 270
Ala Pro Val Val Thr His Thr Tyr Leu Glu Pro Gly Pro Val Thr Ala
        275                 280                 285
Gln Val Val Leu Gln Ala Ala Ile Pro Leu Thr Ser Cys Gly Ser Ser
    290                 295                 300
Pro Val Pro Gly Thr Thr Asp Gly His Arg Pro Thr Ala Glu Ala Pro
305                 310                 315                 320
Asn Thr Thr Ala Gly Gln Val Pro Thr Thr Glu Val Val Gly Thr Thr
                325                 330                 335
Pro Gly Gln Ala Pro Thr Ala Glu Pro Ser Gly Thr Thr Ser Val Gln
            340                 345                 350
Val Pro Thr Thr Glu Val Ile Ser Thr Ala Pro Val Gln Met Pro Thr
        355                 360                 365
Ala Glu Ser Thr Gly Met Thr Pro Glu Lys Val Pro Val Ser Glu Val
    370                 375                 380
Met Gly Thr Thr Leu Ala Glu Met Ser Thr Pro Glu Ala Thr Gly Met
385                 390                 395                 400
Thr Pro Ala Glu Val Ser Ile Val Val Leu Ser Gly Thr Thr Ala Ala
                405                 410                 415
Gln Val Thr Thr Thr Glu Trp Val Glu Thr Thr Ala Arg Glu Leu Pro
            420                 425                 430
Ile Pro Glu Pro Glu Gly Pro Asp Ala Ser Ser Ile Met Ser Thr Glu
        435                 440                 445
Ser Ile Thr Gly Ser Leu Gly Pro Leu Leu Asp Gly Thr Ala Thr Leu
    450                 455                 460
Arg Leu Val Lys Arg Gln Val Pro Leu Asp Cys Val Leu Tyr Arg Tyr
465                 470                 475                 480
Gly Ser Phe Ser Val Thr Leu Asp Ile Val Gln Gly Ile Glu Ser Ala
                485                 490                 495
Glu Ile Leu Gln Ala Val Pro Ser Gly Glu Gly Asp Ala Phe Glu Leu
            500                 505                 510
Thr Val Ser Cys Gln Gly Gly Leu Pro Lys Glu Ala Cys Met Glu Ile
        515                 520                 525
Ser Ser Pro Gly Cys Gln Pro Pro Ala Gln Arg Leu Cys Gln Pro Val
    530                 535                 540
Leu Pro Ser Pro Ala Cys Gln Leu Val Leu His Gln Ile Leu Lys Gly
545                 550                 555                 560
Gly Ser Gly Thr Tyr Cys Leu Asn Val Ser Leu Ala Asp Thr Asn Ser
                565                 570                 575
Leu Ala Val Val Ser Thr Gln Leu Ile Met Pro Gly Gln Glu Ala Gly
            580                 585                 590
Leu Gly Gln Val Pro Leu Ile Val Gly Ile Leu Leu Val Leu Met Ala
        595                 600                 605
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Val Val Leu Ala Ser Leu Ile Tyr Arg Arg Arg Leu Met Lys Gln Asp
    610                 615                 620
Phe Ser Val Pro Gln Leu Pro His Ser Ser Ser His Trp Leu Arg Leu
625                 630                 635                 640
Pro Arg Ile Phe Cys Ser Cys Pro Ile Gly Glu Asn Ser Pro Leu Leu
                645                 650                 655
Ser Gly Gln Gln Val
            660
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<210> 71
<211> 309
<212> PRT
<213> Homo sapiens

<400> 71

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Met Ser Leu Glu Gln Arg Ser Leu His Cys Lys Pro Glu Glu Ala Leu
 1               5                  10                  15
Glu Ala Gln Gln Glu Ala Leu Gly Leu Val Cys Val Gln Ala Ala Thr
            20                  25                  30
Ser Ser Ser Ser Pro Leu Val Leu Gly Thr Leu Glu Glu Val Pro Thr
        35                  40                  45
Ala Gly Ser Thr Asp Pro Pro Gln Ser Pro Gln Gly Ala Ser Ala Phe
    50                  55                  60
Pro Thr Thr Ile Asn Phe Thr Arg Gln Arg Gln Pro Ser Glu Gly Ser
65                  70                  75                  80
Ser Ser Arg Glu Glu Glu Gly Pro Ser Thr Ser Cys Ile Leu Glu Ser
                85                  90                  95
Leu Phe Arg Ala Val Ile Thr Lys Lys Val Ala Asp Leu Val Gly Phe
            100                 105                 110
Leu Leu Leu Lys Tyr Arg Ala Arg Glu Pro Val Thr Lys Ala Glu Met
        115                 120                 125
Leu Glu Ser Val Ile Lys Asn Tyr Lys His Cys Phe Pro Glu Ile Phe
    130                 135                 140
Gly Lys Ala Ser Glu Ser Leu Gln Leu Val Phe Gly Ile Asp Val Lys
145                 150                 155                 160
Glu Ala Asp Pro Thr Gly His Ser Tyr Val Leu Val Thr Cys Leu Gly
                165                 170                 175
Leu Ser Tyr Asp Gly Leu Leu Gly Asp Asn Gln Ile Met Pro Lys Thr
            180                 185                 190
Gly Phe Leu Ile Ile Val Leu Val Met Ile Ala Met Glu Gly Gly His
        195                 200                 205
Ala Pro Glu Glu Glu Ile Trp Glu Glu Leu Ser Val Met Glu Val Tyr
    210                 215                 220
Asp Gly Arg Glu His Ser Ala Tyr Gly Glu Pro Arg Lys Leu Leu Thr
225                 230                 235                 240
Gln Asp Leu Val Gln Glu Lys Tyr Leu Glu Tyr Arg Gln Val Pro Asp
                245                 250                 255
Ser Asp Pro Ala Arg Tyr Glu Phe Leu Trp Gly Pro Arg Ala Leu Ala
            260                 265                 270
Glu Thr Ser Tyr Val Lys Val Leu Glu Tyr Val Ile Lys Val Ser Ala
        275                 280                 285
Arg Val Arg Phe Phe Phe Pro Ser Leu Arg Glu Ala Ala Leu Arg Glu
    290                 295                 300
Glu Glu Glu Gly Val
305
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<210> 72
<211> 314
<212> PRT
<213> Homo sapiens

<400> 72
Met Pro Leu Glu Gln Arg Ser Gln His Cys Lys Pro Glu Glu Gly Leu
1 5 10 15
Glu Ala Arg Gly Glu Ala Leu Gly Leu Val Gly Ala Gln Ala Pro Ala
20 25 30
Thr Glu Glu Gln Gln Thr Ala Ser Ser Ser Ser Thr Leu Val Glu Val
35 40 45
Thr Leu Gly Glu Val Pro Ala Ala Asp Ser Pro Ser Pro Pro His Ser
50 55 60
Pro Gln Gly Ala Ser Ser Phe Ser Thr Thr Ile Asn Tyr Thr Leu Trp
65 70 75 80
Arg Gln Ser Asp Glu Gly Ser Ser Asn Gln Glu Glu Glu Gly Pro Arg
85 90 95
Met Phe Pro Asp Leu Glu Ser Glu Phe Gln Ala Ala Ile Ser Arg Lys
100 105 110
Met Val Glu Leu Val His Phe Leu Leu Leu Lys Tyr Arg Ala Arg Glu
115 120 125
Pro Val Thr Lys Ala Glu Met Leu Glu Ser Val Leu Arg Asn Cys Gln
130 135 140
Asp Phe Phe Pro Val Ile Phe Ser Lys Ala Ser Glu Tyr Leu Gln Leu
145 150 155 160
Val Phe Gly Ile Glu Val Val Glu Val Val Pro Ile Ser His Leu Tyr
165 170 175
Ile Leu Val Thr Cys Leu Gly Leu Ser Tyr Asp Gly Leu Leu Gly Asp
180 185 190
Asn Gln Val Met Pro Lys Thr Gly Leu Leu Ile Ile Val Leu Ala Ile
195 200 205
Ile Ala Ile Glu Gly Asp Cys Ala Pro Glu Glu Lys Ile Trp Glu Glu
210 215 220
Leu Ser Met Leu Glu Val Phe Glu Gly Arg Glu Asp Ser Val Phe Ala
225 230 235 240
His Pro Arg Lys Leu Leu Met Gln Asp Leu Val Gln Glu Asn Tyr Leu
245 250 255
Glu Tyr Arg Gln Val Pro Gly Ser Asp Pro Ala Cys Tyr Glu Phe Leu
260 265 270
Trp Gly Pro Arg Ala Leu Ile Glu Thr Ser Tyr Val Lys Val Leu His
275 280 285
His Thr Leu Lys Ile Gly Gly Glu Pro His Ile Ser Tyr Pro Pro Leu
290 295 300
His Glu Arg Ala Leu Arg Glu Gly Glu Glu
305 310

<210> 73
<211> 314
<212> PRT
<213> Homo sapiens

<400> 73
Met Pro Leu Glu Gln Arg Ser Gln His Cys Lys Pro Glu Glu Gly Leu
1 5 10 15

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Glu Ala Arg Gly Glu Ala Leu Gly Leu Val Gly Ala Gln Ala Pro Ala
            20                  25                  30
Thr Glu Glu Gln Glu Ala Ala Ser Ser Ser Ser Thr Leu Val Glu Val
        35                  40                  45
Thr Leu Gly Glu Val Pro Ala Ala Glu Ser Pro Asp Pro Pro Gln Ser
    50                  55                  60
Pro Gln Gly Ala Ser Ser Leu Pro Thr Thr Met Asn Tyr Pro Leu Trp
65                  70                  75                  80
Ser Gln Ser Tyr Glu Asp Ser Ser Asn Gln Glu Glu Glu Gly Pro Ser
                85                  90                  95
Thr Phe Pro Asp Leu Glu Ser Glu Phe Gln Ala Ala Leu Ser Arg Lys
            100                 105                 110
Val Ala Glu Leu Val His Phe Leu Leu Leu Lys Tyr Arg Ala Arg Glu
        115                 120                 125
Pro Val Thr Lys Ala Glu Met Leu Gly Ser Val Val Gly Asn Trp Gln
    130                 135                 140
Tyr Phe Phe Pro Val Ile Phe Ser Lys Ala Ser Ser Ser Leu Gln Leu
145                 150                 155                 160
Val Phe Gly Ile Glu Leu Met Glu Val Asp Pro Ile Gly His Leu Tyr
                165                 170                 175
Ile Phe Ala Thr Cys Leu Gly Leu Ser Tyr Asp Gly Leu Leu Gly Asp
            180                 185                 190
Asn Gln Ile Met Pro Lys Ala Gly Leu Leu Ile Ile Val Leu Ala Ile
        195                 200                 205
Ile Ala Arg Glu Gly Asp Cys Ala Pro Glu Glu Lys Ile Trp Glu Glu
    210                 215                 220
Leu Ser Val Leu Glu Val Phe Glu Gly Arg Glu Asp Ser Ile Leu Gly
225                 230                 235                 240
Asp Pro Lys Lys Leu Leu Thr Gln His Phe Val Gln Glu Asn Tyr Leu
                245                 250                 255
Glu Tyr Arg Gln Val Pro Gly Ser Asp Pro Ala Cys Tyr Glu Phe Leu
            260                 265                 270
Trp Gly Pro Arg Ala Leu Val Glu Thr Ser Tyr Val Lys Val Leu His
        275                 280                 285
His Met Val Lys Ile Ser Gly Gly Pro His Ile Ser Tyr Pro Pro Leu
    290                 295                 300
His Glu Trp Val Leu Arg Glu Gly Glu Glu
305                 310
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<210> 74
<211> 180
<212> PRT
<213> Homo sapiens

<400> 74

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Met Gln Ala Glu Gly Arg Gly Thr Gly Gly Ser Thr Gly Asp Ala Asp
 1               5                  10                  15
Gly Pro Gly Gly Pro Gly Ile Pro Asp Gly Pro Gly Gly Asn Ala Gly
            20                  25                  30
Gly Pro Gly Glu Ala Gly Ala Thr Gly Gly Arg Gly Pro Arg Gly Ala
        35                  40                  45
Gly Ala Ala Arg Ala Ser Gly Pro Gly Gly Gly Ala Pro Arg Gly Pro
    50                  55                  60
His Gly Gly Ala Ala Ser Gly Leu Asn Gly Cys Cys Arg Cys Gly Ala
65                  70                  75                  80
Arg Gly Pro Glu Ser Arg Leu Leu Glu Phe Tyr Leu Ala Met Pro Phe
```

```
                85                  90                  95
Ala Thr Pro Met Glu Ala Glu Leu Ala Arg Arg Ser Leu Ala Gln Asp
            100                 105                 110
Ala Pro Pro Leu Pro Val Pro Gly Val Leu Leu Lys Glu Phe Thr Val
        115                 120                 125
Ser Gly Asn Ile Leu Thr Ile Arg Leu Thr Ala Ala Asp His Arg Gln
    130                 135                 140
Leu Gln Leu Ser Ile Ser Ser Cys Leu Gln Gln Leu Ser Leu Leu Met
145                 150                 155                 160
Trp Ile Thr Gln Cys Phe Leu Pro Val Phe Leu Ala Gln Pro Pro Ser
                165                 170                 175
Gly Gln Arg Arg
            180
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<210> 75
<211> 180
<212> PRT
<213> Homo sapiens

<400> 75

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Met Gln Ala Glu Gly Arg Gly Thr Gly Gly Ser Thr Gly Asp Ala Asp
 1               5                  10                  15
Gly Pro Gly Gly Pro Gly Ile Pro Asp Gly Pro Gly Gly Asn Ala Gly
            20                  25                  30
Gly Pro Gly Glu Ala Gly Ala Thr Gly Gly Arg Gly Pro Arg Gly Ala
        35                  40                  45
Gly Ala Ala Arg Ala Ser Gly Pro Arg Gly Gly Ala Pro Arg Gly Pro
    50                  55                  60
His Gly Gly Ala Ala Ser Ala Gln Asp Gly Arg Cys Pro Cys Gly Ala
65                  70                  75                  80
Arg Arg Pro Asp Ser Arg Leu Leu Glu Leu His Ile Thr Met Pro Phe
                85                  90                  95
Ser Ser Pro Met Glu Ala Glu Leu Val Arg Arg Ile Leu Ser Arg Asp
            100                 105                 110
Ala Ala Pro Leu Pro Arg Pro Gly Ala Val Leu Lys Asp Phe Thr Val
        115                 120                 125
Ser Gly Asn Leu Leu Phe Ile Arg Leu Thr Ala Ala Asp His Arg Gln
    130                 135                 140
Leu Gln Leu Ser Ile Ser Ser Cys Leu Gln Gln Leu Ser Leu Leu Met
145                 150                 155                 160
Trp Ile Thr Gln Cys Phe Leu Pro Val Phe Leu Ala Gln Ala Pro Ser
                165                 170                 175
Gly Gln Arg Arg
            180
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<210> 76
<211> 210
<212> PRT
<213> Homo sapiens

<400> 76

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Met Gln Ala Glu Gly Arg Gly Thr Gly Gly Ser Thr Gly Asp Ala Asp
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Gly Pro Gly Gly Pro Gly Ile Pro Asp Gly Pro Gly Gly Asn Ala Gly
            20                  25                  30
```

```
Gly Pro Gly Glu Ala Gly Ala Thr Gly Gly Arg Gly Pro Arg Gly Ala
        35                  40                  45
Gly Ala Ala Arg Ala Ser Gly Pro Arg Gly Gly Ala Pro Arg Gly Pro
    50                  55                  60
His Gly Gly Ala Ala Ser Ala Gln Asp Gly Arg Cys Pro Cys Gly Ala
65                  70                  75                  80
Arg Arg Pro Asp Ser Arg Leu Leu Glu Leu His Ile Thr Met Pro Phe
                85                  90                  95
Ser Ser Pro Met Glu Ala Glu Leu Val Arg Arg Ile Leu Ser Arg Asp
            100                 105                 110
Ala Ala Pro Leu Pro Arg Pro Gly Ala Val Leu Lys Asp Phe Thr Val
        115                 120                 125
Ser Gly Asn Leu Leu Phe Met Ser Val Trp Asp Gln Asp Arg Glu Gly
    130                 135                 140
Ala Gly Arg Met Arg Val Val Gly Trp Gly Leu Gly Ser Ala Ser Pro
145                 150                 155                 160
Glu Gly Gln Lys Ala Arg Asp Leu Arg Thr Pro Lys His Lys Val Ser
                165                 170                 175
Glu Gln Arg Pro Gly Thr Pro Gly Pro Pro Pro Pro Glu Gly Ala Gln
            180                 185                 190
Gly Asp Gly Cys Arg Gly Val Ala Phe Asn Val Met Phe Ser Ala Pro
        195                 200                 205
His Ile
    210
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<210> 77
<211> 509
<212> PRT
<213> Homo sapiens

<400> 77

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Met Glu Arg Arg Arg Leu Trp Gly Ser Ile Gln Ser Arg Tyr Ile Ser
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Met Ser Val Trp Thr Ser Pro Arg Arg Leu Val Glu Leu Ala Gly Gln
            20                  25                  30
Ser Leu Leu Lys Asp Glu Ala Leu Ala Ile Ala Ala Leu Glu Leu Leu
        35                  40                  45
Pro Arg Glu Leu Phe Pro Pro Leu Phe Met Ala Ala Phe Asp Gly Arg
    50                  55                  60
His Ser Gln Thr Leu Lys Ala Met Val Gln Ala Trp Pro Phe Thr Cys
65                  70                  75                  80
Leu Pro Leu Gly Val Leu Met Lys Gly Gln His Leu His Leu Glu Thr
                85                  90                  95
Phe Lys Ala Val Leu Asp Gly Leu Asp Val Leu Leu Ala Gln Glu Val
            100                 105                 110
Arg Pro Arg Arg Trp Lys Leu Gln Val Leu Asp Leu Arg Lys Asn Ser
        115                 120                 125
His Gln Asp Phe Trp Thr Val Trp Ser Gly Asn Arg Ala Ser Leu Tyr
    130                 135                 140
Ser Phe Pro Glu Pro Glu Ala Ala Gln Pro Met Thr Lys Lys Arg Lys
145                 150                 155                 160
Val Asp Gly Leu Ser Thr Glu Ala Glu Gln Pro Phe Ile Pro Val Glu
                165                 170                 175
Val Leu Val Asp Leu Phe Leu Lys Glu Gly Ala Cys Asp Glu Leu Phe
            180                 185                 190
Ser Tyr Leu Ile Glu Lys Val Lys Arg Lys Lys Asn Val Leu Arg Leu
```

```
        195                 200                 205
Cys Cys Lys Lys Leu Lys Ile Phe Ala Met Pro Met Gln Asp Ile Lys
    210                 215                 220
Met Ile Leu Lys Met Val Gln Leu Asp Ser Ile Glu Asp Leu Glu Val
225                 230                 235                 240
Thr Cys Thr Trp Lys Leu Pro Thr Leu Ala Lys Phe Ser Pro Tyr Leu
                245                 250                 255
Gly Gln Met Ile Asn Leu Arg Arg Leu Leu Leu Ser His Ile His Ala
            260                 265                 270
Ser Ser Tyr Ile Ser Pro Glu Lys Glu Glu Gln Tyr Ile Ala Gln Phe
        275                 280                 285
Thr Ser Gln Phe Leu Ser Leu Gln Cys Leu Gln Ala Leu Tyr Val Asp
    290                 295                 300
Ser Leu Phe Phe Leu Arg Gly Arg Leu Asp Gln Leu Leu Arg His Val
305                 310                 315                 320
Met Asn Pro Leu Glu Thr Leu Ser Ile Thr Asn Cys Arg Leu Ser Glu
                325                 330                 335
Gly Asp Val Met His Leu Ser Gln Ser Pro Ser Val Ser Gln Leu Ser
            340                 345                 350
Val Leu Ser Leu Ser Gly Val Met Leu Thr Asp Val Ser Pro Glu Pro
        355                 360                 365
Leu Gln Ala Leu Leu Glu Arg Ala Ser Ala Thr Leu Gln Asp Leu Val
    370                 375                 380
Phe Asp Glu Cys Gly Ile Thr Asp Asp Gln Leu Leu Ala Leu Leu Pro
385                 390                 395                 400
Ser Leu Ser His Cys Ser Gln Leu Thr Thr Leu Ser Phe Tyr Gly Asn
                405                 410                 415
Ser Ile Ser Ile Ser Ala Leu Gln Ser Leu Leu Gln His Leu Ile Gly
            420                 425                 430
Leu Ser Asn Leu Thr His Val Leu Tyr Pro Val Pro Leu Glu Ser Tyr
        435                 440                 445
Glu Asp Ile His Gly Thr Leu His Leu Glu Arg Leu Ala Tyr Leu His
    450                 455                 460
Ala Arg Leu Arg Glu Leu Leu Cys Glu Leu Gly Arg Pro Ser Met Val
465                 470                 475                 480
Trp Leu Ser Ala Asn Pro Cys Pro His Cys Gly Asp Arg Thr Phe Tyr
                485                 490                 495
Asp Pro Glu Pro Ile Leu Cys Pro Cys Phe Met Pro Asn
            500                 505
```

<210> 78
<211> 261
<212> PRT
<213> Homo sapiens

<400> 78

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Met Trp Val Pro Val Val Phe Leu Thr Leu Ser Val Thr Trp Ile Gly
 1               5                  10                  15
Ala Ala Pro Leu Ile Leu Ser Arg Ile Val Gly Gly Trp Glu Cys Glu
            20                  25                  30
Lys His Ser Gln Pro Trp Gln Val Leu Val Ala Ser Arg Gly Arg Ala
        35                  40                  45
Val Cys Gly Gly Val Leu Val His Pro Gln Trp Val Leu Thr Ala Ala
    50                  55                  60
His Cys Ile Arg Asn Lys Ser Val Ile Leu Leu Gly Arg His Ser Leu
65                  70                  75                  80
```

```
Phe His Pro Glu Asp Thr Gly Gln Val Phe Gln Val Ser His Ser Phe
                85                  90                  95
Pro His Pro Leu Tyr Asp Met Ser Leu Leu Lys Asn Arg Phe Leu Arg
            100                 105                 110
Pro Gly Asp Asp Ser Ser His Asp Leu Met Leu Leu Arg Leu Ser Glu
        115                 120                 125
Pro Ala Glu Leu Thr Asp Ala Val Lys Val Met Asp Leu Pro Thr Gln
    130                 135                 140
Glu Pro Ala Leu Gly Thr Thr Cys Tyr Ala Ser Gly Trp Gly Ser Ile
145                 150                 155                 160
Glu Pro Glu Glu Phe Leu Thr Pro Lys Lys Leu Gln Cys Val Asp Leu
                165                 170                 175
His Val Ile Ser Asn Asp Val Cys Ala Gln Val His Pro Gln Lys Val
            180                 185                 190
Thr Lys Phe Met Leu Cys Ala Gly Arg Trp Thr Gly Gly Lys Ser Thr
        195                 200                 205
Cys Ser Gly Asp Ser Gly Gly Pro Leu Val Cys Asn Gly Val Leu Gln
    210                 215                 220
Gly Ile Thr Ser Trp Gly Ser Glu Pro Cys Ala Leu Pro Glu Arg Pro
225                 230                 235                 240
Ser Leu Tyr Thr Lys Val Val His Tyr Arg Lys Trp Ile Lys Asp Thr
                245                 250                 255
Ile Val Ala Asn Pro
            260
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<210> 79
<211> 123
<212> PRT
<213> Homo sapiens

<400> 79

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Met Lys Ala Val Leu Leu Ala Leu Leu Met Ala Gly Leu Ala Leu Gln
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Pro Gly Thr Ala Leu Leu Cys Tyr Ser Cys Lys Ala Gln Val Ser Asn
            20                  25                  30
Glu Asp Cys Leu Gln Val Glu Asn Cys Thr Gln Leu Gly Glu Gln Cys
        35                  40                  45
Trp Thr Ala Arg Ile Arg Ala Val Gly Leu Leu Thr Val Ile Ser Lys
    50                  55                  60
Gly Cys Ser Leu Asn Cys Val Asp Asp Ser Gln Asp Tyr Tyr Val Gly
65                  70                  75                  80
Lys Lys Asn Ile Thr Cys Cys Asp Thr Asp Leu Cys Asn Ala Ser Gly
                85                  90                  95
Ala His Ala Leu Gln Pro Ala Ala Ala Ile Leu Ala Leu Leu Pro Ala
            100                 105                 110
Leu Gly Leu Leu Leu Trp Gly Pro Gly Gln Leu
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<211> 2817
<212> DNA
<213> Homo sapiens

<400> 80

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<212> DNA
<213> Homo sapiens

<400> 81
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<211> 4559
<212> DNA
<213> Homo sapiens

<400> 82
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<212> DNA
<213> Homo sapiens

<400> 83
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<210> 84
<211> 752
<212> DNA
<213> Homo sapiens

<400> 84
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<210> 85
<211> 2148
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(2)
<223> n = A,T,C or G

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<210> 86
<211> 1466
<212> DNA
<213> Homo sapiens

<400> 86
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<210> 87
<211> 990
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(990)
<223> n = A,T,C or G

<400> 87
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<210> 88
<211> 9
<212> PRT
<213> Homo sapiens

<400> 88
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<210> 89
<211> 10
<212> PRT
<213> Homo sapiens

<400> 89
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1 5 10

<210> 90
<211> 9
<212> PRT
<213> Homo sapiens

<400> 90
Leu Ile Tyr Arg Arg Arg Leu Met Lys
1 5

<210> 91
<211> 10
<212> PRT
<213> Homo sapiens

<400> 91
Ser Leu Ile Tyr Arg Arg Arg Leu Met Lys
1 5 10

<210> 92
<211> 8
<212> PRT
<213> Homo sapiens

<400> 92
Ile Tyr Arg Arg Arg Leu Met Lys
1 5

<210> 93
<211> 9
<212> PRT
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<400> 93
Leu Pro His Ser Ser Ser His Trp Leu
1 5

<210> 94
<211> 10
<212> PRT
<213> Homo sapiens

<400> 94
Gln Leu Pro His Ser Ser Ser His Trp Leu
1 5 10

<210> 95

<211> 8
<212> PRT
<213> Homo sapiens

<400> 95
Glu Ser Leu Phe Arg Ala Val Ile
1 5

<210> 96
<211> 10
<212> PRT
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<400> 96
Ile Leu Glu Ser Leu Phe Arg Ala Val Ile
1 5 10

<210> 97
<211> 9
<212> PRT
<213> Homo sapiens

<400> 97
Ile Leu Glu Ser Leu Phe Arg Ala Val
1 5

<210> 98
<211> 10
<212> PRT
<213> Homo sapiens

<400> 98
Cys Ile Leu Glu Ser Leu Phe Arg Ala Val
1 5 10

<210> 99
<211> 9
<212> PRT
<213> Homo sapiens

<400> 99
Cys Ile Leu Glu Ser Leu Phe Arg Ala
1 5

<210> 100
<211> 9
<212> PRT
<213> Homo sapiens

<400> 100
Glu Phe Leu Trp Gly Pro Arg Ala Leu
1 5

<210> 101
<211> 8
<212> PRT
<213> Homo sapiens

<400> 101
Phe Leu Trp Gly Pro Arg Ala Leu
1 5

<210> 102
<211> 10
<212> PRT
<213> Homo sapiens

<400> 102
Phe Leu Trp Gly Pro Arg Ala Leu Ala Glu
1 5 10

<210> 103
<211> 10
<212> PRT
<213> Homo sapiens

<400> 103
Leu Trp Gly Pro Arg Ala Leu Ala Glu Thr
1 5 10

<210> 104
<211> 9
<212> PRT
<213> Homo sapiens

<400> 104
Pro Arg Ala Leu Ala Glu Thr Ser Tyr
1 5

<210> 105
<211> 10
<212> PRT
<213> Homo sapiens

<400> 105
Gly Pro Arg Ala Leu Ala Glu Thr Ser Tyr
1 5 10

<210> 106
<211> 9
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<400> 106
Arg Ala Leu Ala Glu Thr Ser Tyr Val
1 5

<210> 107
<211> 9
<212> PRT
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<400> 107
Leu Ala Glu Thr Ser Tyr Val Lys Val
1 5

<210> 108
<211> 10
<212> PRT
<213> Homo sapiens

<400> 108
Ala Leu Ala Glu Thr Ser Tyr Val Lys Val
1 5 10

<210> 109
<211> 9
<212> PRT
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<400> 109
Ala Glu Thr Ser Tyr Val Lys Val Leu
1 5

<210> 110
<211> 10
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<400> 110
Leu Ala Glu Thr Ser Tyr Val Lys Val Leu
1 5 10

<210> 111
<211> 9
<212> PRT
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<400> 111
Thr Ser Tyr Val Lys Val Leu Glu Tyr
1 5

<210> 112
<211> 10

<212> PRT
<213> Homo sapiens

<400> 112
Glu Thr Ser Tyr Val Lys Val Leu Glu Tyr
1 5 10

<210> 113
<211> 9
<212> PRT
<213> Homo sapiens

<400> 113
Lys Val Leu Glu Tyr Val Ile Lys Val
1 5

<210> 114
<211> 10
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<213> Homo sapiens

<400> 114
Ser Tyr Val Leu Val Thr Cys Leu Gly Leu
1 5 10

<210> 115
<211> 9
<212> PRT
<213> Homo sapiens

<400> 115
Tyr Val Leu Val Thr Cys Leu Gly Leu
1 5

<210> 116
<211> 8
<212> PRT
<213> Homo sapiens

<400> 116
Val Leu Val Thr Cys Leu Gly Leu
1 5

<210> 117
<211> 9
<212> PRT
<213> Homo sapiens

<400> 117
Thr Gln Asp Leu Val Gln Glu Lys Tyr
1 5

<210> 118
<211> 10
<212> PRT
<213> Homo sapiens

<400> 118
Leu Thr Gln Asp Leu Val Gln Glu Lys Tyr
1 5 10

<210> 119
<211> 9
<212> PRT
<213> Homo sapiens

<400> 119
Tyr Gly Glu Pro Arg Lys Leu Leu Thr
1 5

<210> 120
<211> 9
<212> PRT
<213> Homo sapiens

<400> 120
Leu Val Gln Glu Lys Tyr Leu Glu Tyr
1 5

<210> 121
<211> 10
<212> PRT
<213> Homo sapiens

<400> 121
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1 5 10

<210> 122
<211> 9
<212> PRT
<213> Homo sapiens

<400> 122
Ser Ala Tyr Gly Glu Pro Arg Lys Leu
1 5

<210> 123
<211> 9
<212> PRT
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<400> 123

Lys Val Leu Glu Tyr Val Ile Lys Val
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<210> 124
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<210> 578
<211> 9

<212> PRT
<213> Homo sapiens

<400> 578
Lys Ile Met Pro Lys Lys Pro Ala Glu
1 5

<210> 579
<211> 10
<212> PRT
<213> Homo sapiens

<400> 579
Ser Leu Gln Arg Ile Phe Pro Lys Ile Met
1 5 10

<210> 580
<211> 9
<212> PRT
<213> Homo sapiens

<400> 580
Tyr Ile Lys Ser Tyr Leu Glu Gln Ala
1 5

<210> 581
<211> 9
<212> PRT
<213> Homo sapiens

<400> 581
Ser Phe Gln Asp Tyr Ile Lys Ser Tyr
1 5

<210> 582
<211> 10
<212> PRT
<213> Homo sapiens

<400> 582
Asp Ser Phe Gln Asp Tyr Ile Lys Ser Tyr
1 5 10

<210> 583
<211> 8
<212> PRT
<213> Homo sapiens

<400> 583
Leu Pro Glu Glu Lys Gln Pro Leu
1 5

<210> 584
<211> 9
<212> PRT
<213> Homo sapiens

<400> 584
Gln Leu Pro Glu Glu Lys Gln Pro Leu
1 5

<210> 585
<211> 10
<212> PRT
<213> Homo sapiens

<400> 585
Lys Gln Leu Pro Glu Glu Lys Gln Pro Leu
1 5 10

<210> 586
<211> 9
<212> PRT
<213> Homo sapiens

<400> 586
Leu Pro Glu Glu Lys Gln Pro Leu Leu
1 5

<210> 587
<211> 10
<212> PRT
<213> Homo sapiens

<400> 587
Gln Leu Pro Glu Glu Lys Gln Pro Leu Leu
1 5 10

<210> 588
<211> 9
<212> PRT
<213> Homo sapiens

<400> 588
Ser Leu Leu Cys Arg His Lys Arg Lys
1 5

<210> 589
<211> 91
<212> PRT
<213> Homo sapiens

<400> 589

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Glu Val Pro Gln Leu Thr Asp Leu Ser Phe Val Asp Ile Thr Asp Ser
 1               5                  10                  15
Ser Ile Gly Leu Arg Trp Thr Pro Leu Asn Ser Ser Thr Ile Ile Gly
            20                  25                  30
Tyr Arg Ile Thr Val Val Ala Ala Gly Glu Gly Ile Pro Ile Phe Glu
        35                  40                  45
Asp Phe Val Asp Ser Ser Val Gly Tyr Tyr Thr Val Thr Gly Leu Glu
    50                  55                  60
Pro Gly Ile Asp Tyr Asp Ile Ser Val Ile Thr Leu Ile Asn Gly Gly
65                  70                  75                  80
Glu Ser Ala Pro Thr Thr Leu Thr Gln Gln Thr
                85                  90
```

<210> 590
<211> 147
<212> PRT
<213> Homo sapiens

<400> 590

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Cys Thr Phe Asp Asn Leu Ser Pro Gly Leu Glu Tyr Asn Val Ser Val
 1               5                  10                  15
Tyr Thr Val Lys Asp Asp Lys Glu Ser Val Pro Ile Ser Asp Thr Ile
            20                  25                  30
Ile Pro Glu Val Pro Gln Leu Thr Asp Leu Ser Phe Val Asp Ile Thr
        35                  40                  45
Asp Ser Ser Ile Gly Leu Arg Trp Thr Pro Leu Asn Ser Ser Thr Ile
    50                  55                  60
Ile Gly Tyr Arg Ile Thr Val Val Ala Ala Gly Glu Gly Ile Pro Ile
65                  70                  75                  80
Phe Glu Asp Phe Val Asp Ser Ser Val Gly Tyr Tyr Thr Val Thr Gly
                85                  90                  95
Leu Glu Pro Gly Ile Asp Tyr Asp Ile Ser Val Ile Thr Leu Ile Asn
            100                 105                 110
Gly Gly Glu Ser Ala Pro Thr Thr Leu Thr Gln Gln Thr Ala Val Pro
        115                 120                 125
Pro Pro Thr Asp Leu Arg Phe Thr Asn Ile Gly Pro Asp Thr Met Arg
    130                 135                 140
Val Thr Trp
145
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<210> 591
<211> 2823
<212> DNA
<213> Homo sapiens

<400> 591

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ggatgacaag gaaagtgtcc ctatctctga taccatcatc ccaggtaata gaaaataagc 120
tgctatcctg agagtgacat tccaataaga gtggggatta gcatcttaat ccccagatgc 180
ttaagggtgt caactatatt tgggatttaa ttccgatctc ccagctgcac tttccaaaac 240
caagaagtca aagcagcgat ttggacaaaa tgcttgctgt taacactgct ttactgtctg 300
tgcttcactg ggatgctgtg tgttgcagcg agtatgtaat ggagtggcag ccatggcttt 360
aactctgtat tgtctgctca catggaagta tgactaaaac actgtcacgt gtctgtactc 420
agtactgata ggctcaaagt aatatggtaa atgcatccca tcagtacatt tctgcccgat 480
tttacaatcc atatcaattt ccaacagctg cctatttcat cttgcagttt caaatccttc 540
```

```
tttttgaaaa ttggatttta aaaaaaagtt aagtaaaagt cacaccttca gggttgttct 600
ttcttgtggc cttgaaagac aacattgcaa aggcctgtcc taaggatagg cttgtttgtc 660
cattgggtta taacataatg aaagcattgg acagatcgtg tccccctttg gactcttcag 720
tagaatgctt ttactaacgc taattacatg ttttgattat gaatgaacct aaaatagtgg 780
caatggcctt aacctaggcc tgtctttcct cagcctgaat gtgcttttga atggcacatt 840
tcacaccata cattcataat gcattagcgt tatggccatg atgttgtcat gagttttgta 900
tgggagaaaa aaaatcaatt tatcacccat ttattatttt ttccggttgt tcatgcaagc 960
ttatttttcta ctaaaacagt tttggaatta ttaaaagcat tgctgatact tacttcagat 1020
attatgtcta ggctctaaga atggtttcga catcctaaac agccatatga tttttaggaa 1080
tctgaacagt tcaaattgta ccctttaagg atgttttcaa aatgtaaaaa atatatatat 1140
atatatatat tccctaaaag aatattcctg tttattcttc tagggaagca aactgttcat 1200
gatgcttagg aagtcttttc agagaattta aaacagattg catattacca tcattgcttt 1260
aacattccac caattttact actagtaacc tgatatacac tgctttattt tttcctcttt 1320
ttttccctct attttccttt tgcctccccc tccctttgct ttgtaactca atagaggtgc 1380
cccaactcac tgacctaagc tttgttgata taaccgattc aagcatcggc ctgaggtgga 1440
ccccgctaaa ctcttccacc attattgggt accgcatcac agtagttgcg gcaggagaag 1500
gtatccctat ttttgaagat tttgtggact cctcagtagg atactacaca gtcacagggc 1560
tggagccggg cattgactat gatatcagcg ttatcactct cattaatggc ggcgagagtg 1620
cccctactac actgacacaa caaacgggtg aattttgaaa acttctgcgt ttgagacata 1680
gatggtgttg catgctgcca ccagttactc cggttaaata tggatgtttc atgggggaag 1740
tcagcaattg gccaaagatt cagataggtg gaattggggg gataaggaat caaatgcatc 1800
tgctaaactg attggagaaa aacacatgca atatcttcag tacactctca tttaaaccac 1860
aagtagatat aaagcctaga gaaatacaga tgtctgctct gttaaatata aaatagcaaa 1920
tgttcattca atttgaagac ctagaatttt tcttcttaaa taccaaacac gaataccaaa 1980
ttgcgtaagt accaattgat aagaatatat caccaaaatg taccatcatg ctcttccttc 2040
taccctttga taaactctac catgctcctt ctttgtagct aaaaacccat caaaatttag 2100
ggtagagtgg atgggcattg ttttgaggta ggagaaaagt aaacttggga ccattctagg 2160
ttttgttgct gtcactaggt aaagaaacac ctctttaacc acagtctggg gacaagcatg 2220
caacatttta aaggttctct gctgtgcatg ggaaaagaaa catgctgaga accaatttgc 2280
atgaacatgt tcacttgtaa gtagaattca ctgaatggaa ctgtagctct agatatctca 2340
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ctttttaaa tatatcaatg atggcaaaaa ggttaaaggg ggcctaacag tactgtgtgt 2580
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ggg                                                              2823
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<210> 592
<211> 702
<212> PRT
<213> Homo sapiens

<400> 592

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Met Glu Ser Pro Ser Ala Pro Pro His Arg Trp Cys Ile Pro Trp Gln
 1               5                  10                  15
Arg Leu Leu Leu Thr Ala Ser Leu Leu Thr Phe Trp Asn Pro Pro Thr
            20                  25                  30
Thr Ala Lys Leu Thr Ile Glu Ser Thr Pro Phe Asn Val Ala Glu Gly
        35                  40                  45
Lys Glu Val Leu Leu Leu Val His Asn Leu Pro Gln His Leu Phe Gly
    50                  55                  60
Tyr Ser Trp Tyr Lys Gly Glu Arg Val Asp Gly Asn Arg Gln Ile Ile
65                  70                  75                  80
Gly Tyr Val Ile Gly Thr Gln Gln Ala Thr Pro Gly Pro Ala Tyr Ser
```

```
                85                  90                  95
Gly Arg Glu Ile Ile Tyr Pro Asn Ala Ser Leu Leu Ile Gln Asn Ile
            100                 105                 110
Ile Gln Asn Asp Thr Gly Phe Tyr Thr Leu His Val Ile Lys Ser Asp
        115                 120                 125
Leu Val Asn Glu Glu Ala Thr Gly Gln Phe Arg Val Tyr Pro Glu Leu
    130                 135                 140
Pro Lys Pro Ser Ile Ser Ser Asn Asn Ser Lys Pro Val Glu Asp Lys
145                 150                 155                 160
Asp Ala Val Ala Phe Thr Cys Glu Pro Glu Thr Gln Asp Ala Thr Tyr
                165                 170                 175
Leu Trp Trp Val Asn Asn Gln Ser Leu Pro Val Ser Pro Arg Leu Gln
            180                 185                 190
Leu Ser Asn Gly Asn Arg Thr Leu Thr Leu Phe Asn Val Thr Arg Asn
        195                 200                 205
Asp Thr Ala Ser Tyr Lys Cys Glu Thr Gln Asn Pro Val Ser Ala Arg
    210                 215                 220
Arg Ser Asp Ser Val Ile Leu Asn Val Leu Tyr Gly Pro Asp Ala Pro
225                 230                 235                 240
Thr Ile Ser Pro Leu Asn Thr Ser Tyr Arg Ser Gly Glu Asn Leu Asn
                245                 250                 255
Leu Ser Cys His Ala Ala Ser Asn Pro Pro Ala Gln Tyr Ser Trp Phe
            260                 265                 270
Val Asn Gly Thr Phe Gln Gln Ser Thr Gln Glu Leu Phe Ile Pro Asn
        275                 280                 285
Ile Thr Val Asn Asn Ser Gly Ser Tyr Thr Cys Gln Ala His Asn Ser
    290                 295                 300
Asp Thr Gly Leu Asn Arg Thr Thr Val Thr Thr Ile Thr Val Tyr Ala
305                 310                 315                 320
Glu Pro Pro Lys Pro Phe Ile Thr Ser Asn Asn Ser Asn Pro Val Glu
                325                 330                 335
Asp Glu Asp Ala Val Ala Leu Thr Cys Glu Pro Glu Ile Gln Asn Thr
            340                 345                 350
Thr Tyr Leu Trp Trp Val Asn Asn Gln Ser Leu Pro Val Ser Pro Arg
        355                 360                 365
Leu Gln Leu Ser Asn Asp Asn Arg Thr Leu Thr Leu Leu Ser Val Thr
    370                 375                 380
Arg Asn Asp Val Gly Pro Tyr Glu Cys Gly Ile Gln Asn Glu Leu Ser
385                 390                 395                 400
Val Asp His Ser Asp Pro Val Ile Leu Asn Val Leu Tyr Gly Pro Asp
                405                 410                 415
Asp Pro Thr Ile Ser Pro Ser Tyr Thr Tyr Tyr Arg Pro Gly Val Asn
            420                 425                 430
Leu Ser Leu Ser Cys His Ala Ala Ser Asn Pro Pro Ala Gln Tyr Ser
        435                 440                 445
Trp Leu Ile Asp Gly Asn Ile Gln Gln His Thr Gln Glu Leu Phe Ile
    450                 455                 460
Ser Asn Ile Thr Glu Lys Asn Ser Gly Leu Tyr Thr Cys Gln Ala Asn
465                 470                 475                 480
Asn Ser Ala Ser Gly His Ser Arg Thr Thr Val Lys Thr Ile Thr Val
                485                 490                 495
Ser Ala Glu Leu Pro Lys Pro Ser Ile Ser Ser Asn Asn Ser Lys Pro
            500                 505                 510
Val Glu Asp Lys Asp Ala Val Ala Phe Thr Cys Glu Pro Glu Ala Gln
        515                 520                 525
Asn Thr Thr Tyr Leu Trp Trp Val Asn Gly Gln Ser Leu Pro Val Ser
    530                 535                 540
```

```
Pro Arg Leu Gln Leu Ser Asn Gly Asn Arg Thr Leu Thr Leu Phe Asn
545                 550                 555                 560
Val Thr Arg Asn Asp Ala Arg Ala Tyr Val Cys Gly Ile Gln Asn Ser
                565                 570                 575
Val Ser Ala Asn Arg Ser Asp Pro Val Thr Leu Asp Val Leu Tyr Gly
            580                 585                 590
Pro Asp Thr Pro Ile Ile Ser Pro Pro Asp Ser Ser Tyr Leu Ser Gly
        595                 600                 605
Ala Asn Leu Asn Leu Ser Cys His Ser Ala Ser Asn Pro Ser Pro Gln
    610                 615                 620
Tyr Ser Trp Arg Ile Asn Gly Ile Pro Gln Gln His Thr Gln Val Leu
625                 630                 635                 640
Phe Ile Ala Lys Ile Thr Pro Asn Asn Asn Gly Thr Tyr Ala Cys Phe
                645                 650                 655
Val Ser Asn Leu Ala Thr Gly Arg Asn Asn Ser Ile Val Lys Ser Ile
            660                 665                 670
Thr Val Ser Ala Ser Gly Thr Ser Pro Gly Leu Ser Ala Gly Ala Thr
        675                 680                 685
Val Gly Ile Met Ile Gly Val Leu Val Gly Val Ala Leu Ile
    690                 695                 700
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<210> 593
<211> 2974
<212> DNA
<213> Homo sapiens

<400> 593

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ctcagggcag agggaggaag gacagcagac cagacagtca cagcagcctt gacaaaacgt 60
tcctggaact caagctcttc tccacagagg aggacagagc agacagcaga gaccatggag 120
tctccctcgg cccctcccca cagatggtgc atcccctggc agaggctcct gctcacagcc 180
tcacttctaa ccttctggaa cccgcccacc actgccaagc tcactattga atccacgccg 240
ttcaatgtcg cagaggggaa ggaggtgctt ctacttgtcc acaatctgcc ccagcatctt 300
tttggctaca gctggtacaa aggtgaaaga gtggatggca accgtcaaat tataggatat 360
gtaataggaa ctcaacaagc taccccaggg cccgcataca gtggtcgaga gataatatac 420
cccaatgcat ccctgctgat ccagaacatc atccagaatg acacaggatt ctacacccta 480
cacgtcataa agtcagatct tgtgaatgaa gaagcaactg gccagttccg ggtatacccg 540
gagctgccca agccctccat ctccagcaac aactccaaac ccgtggagga caaggatgct 600
gtggccttca cctgtgaacc tgagactcag gacgcaacct acctgtggtg ggtaaacaat 660
cagagcctcc cggtcagtcc caggctgcag ctgtccaatg gcaacaggac cctcactcta 720
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gccaggcgca gtgattcagt catcctgaat gtcctctatg gcccggatgc ccccaccatt 840
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tctaacccac ctgcacagta ctcttggttt gtcaatggga ctttccagca atccacccaa 960
gagctcttta tccccaacat cactgtgaat aatagtggat cctatacgtg ccaagcccat 1020
aactcagaca ctggcctcaa taggaccaca gtcacgacga tcacagtcta tgcagagcca 1080
cccaaaccct tcatcaccag caacaactcc aaccccgtgg aggatgagga tgctgtagcc 1140
ttaacctgtg aacctgagat tcagaacaca acctacctgt ggtgggtaaa taatcagagc 1200
ctcccggtca gtcccaggct gcagctgtcc aatgacaaca ggaccctcac tctactcagt 1260
gtcacaagga atgatgtagg accctatgag tgtggaatcc agaacgaatt aagtgttgac 1320
cacagcgacc cagtcatcct gaatgtcctc tatggcccag acgaccccac catttccccc 1380
tcatacacct attaccgtcc aggggtgaac ctcagcctct cctgccatgc agcctctaac 1440
ccacctgcac agtattcttg gctgattgat gggaacatcc agcaacacac acaagagctc 1500
tttatctcca acatcactga gaagaacagc ggactctata cctgccaggc caataactca 1560
gccagtggcc acagcaggac tacagtcaag acaatcacag tctctgcgga gctgcccaag 1620
ccctccatct ccagcaacaa ctccaaaccc gtggaggaca aggatgctgt ggccttcacc 1680
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gacccagtca ccctggatgt cctctatggg ccggacaccc ccatcatttc ccccccagac 1920
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taattaattt catgggacta aatgaactaa tgaggattgc tgattcttta aatgtcttgt 2760
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aaatatactt ttgtgaacaa aaattgagac atttacattt tctccctatg tggtcgctcc 2880
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tcaataaaaa tctgctcttt gtataacaga aaaa                              2974

<210> 594
<211> 1255
<212> PRT
<213> Homo sapiens

<400> 594
Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu
 1               5                  10                  15
Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys
            20                  25                  30
Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His
        35                  40                  45
Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr
    50                  55                  60
Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
65                  70                  75                  80
Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu
                85                  90                  95
Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr
            100                 105                 110
Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro
        115                 120                 125
Val Thr Gly Ala Ser Pro Gly Gly Leu Arg Glu Leu Gln Leu Arg Ser
    130                 135                 140
Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln
145                 150                 155                 160
Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn
                165                 170                 175
Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys
            180                 185                 190
His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser
        195                 200                 205
Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys
    210                 215                 220
Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys
```

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225                 230                 235                 240
Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu
                245                 250                 255
His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val
            260                 265                 270
Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg
        275                 280                 285
Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu
    290                 295                 300
Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln
305                 310                 315                 320
Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys
                325                 330                 335
Pro Cys Ala Arg Val Cys Tyr Gly Leu Gly Met Glu His Leu Arg Glu
            340                 345                 350
Val Arg Ala Val Thr Ser Ala Asn Ile Gln Glu Phe Ala Gly Cys Lys
        355                 360                 365
Lys Ile Phe Gly Ser Leu Ala Phe Leu Pro Glu Ser Phe Asp Gly Asp
    370                 375                 380
Pro Ala Ser Asn Thr Ala Pro Leu Gln Pro Glu Gln Leu Gln Val Phe
385                 390                 395                 400
Glu Thr Leu Glu Glu Ile Thr Gly Tyr Leu Tyr Ile Ser Ala Trp Pro
                405                 410                 415
Asp Ser Leu Pro Asp Leu Ser Val Phe Gln Asn Leu Gln Val Ile Arg
            420                 425                 430
Gly Arg Ile Leu His Asn Gly Ala Tyr Ser Leu Thr Leu Gln Gly Leu
        435                 440                 445
Gly Ile Ser Trp Leu Gly Leu Arg Ser Leu Arg Glu Leu Gly Ser Gly
    450                 455                 460
Leu Ala Leu Ile His His Asn Thr His Leu Cys Phe Val His Thr Val
465                 470                 475                 480
Pro Trp Asp Gln Leu Phe Arg Asn Pro His Gln Ala Leu Leu His Thr
                485                 490                 495
Ala Asn Arg Pro Glu Asp Glu Cys Val Gly Glu Gly Leu Ala Cys His
            500                 505                 510
Gln Leu Cys Ala Arg Gly His Cys Trp Gly Pro Gly Pro Thr Gln Cys
        515                 520                 525
Val Asn Cys Ser Gln Phe Leu Arg Gly Gln Glu Cys Val Glu Glu Cys
    530                 535                 540
Arg Val Leu Gln Gly Leu Pro Arg Glu Tyr Val Asn Ala Arg His Cys
545                 550                 555                 560
Leu Pro Cys His Pro Glu Cys Gln Pro Gln Asn Gly Ser Val Thr Cys
                565                 570                 575
Phe Gly Pro Glu Ala Asp Gln Cys Val Ala Cys Ala His Tyr Lys Asp
            580                 585                 590
Pro Pro Phe Cys Val Ala Arg Cys Pro Ser Gly Val Lys Pro Asp Leu
        595                 600                 605
Ser Tyr Met Pro Ile Trp Lys Phe Pro Asp Glu Glu Gly Ala Cys Gln
    610                 615                 620
Pro Cys Pro Ile Asn Cys Thr His Ser Cys Val Asp Leu Asp Asp Lys
625                 630                 635                 640
Gly Cys Pro Ala Glu Gln Arg Ala Ser Pro Leu Thr Ser Ile Val Ser
                645                 650                 655
Ala Val Val Gly Ile Leu Leu Val Val Val Leu Gly Val Val Phe Gly
            660                 665                 670
Ile Leu Ile Lys Arg Arg Gln Gln Lys Ile Arg Lys Tyr Thr Met Arg
        675                 680                 685
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Arg Leu Leu Gln Glu Thr Glu Leu Val Glu Pro Leu Thr Pro Ser Gly
    690                 695                 700
Ala Met Pro Asn Gln Ala Gln Met Arg Ile Leu Lys Glu Thr Glu Leu
705                 710                 715                 720
Arg Lys Val Lys Val Leu Gly Ser Gly Ala Phe Gly Thr Val Tyr Lys
                725                 730                 735
Gly Ile Trp Ile Pro Asp Gly Glu Asn Val Lys Ile Pro Val Ala Ile
            740                 745                 750
Lys Val Leu Arg Glu Asn Thr Ser Pro Lys Ala Asn Lys Glu Ile Leu
        755                 760                 765
Asp Glu Ala Tyr Val Met Ala Gly Val Gly Ser Pro Tyr Val Ser Arg
    770                 775                 780
Leu Leu Gly Ile Cys Leu Thr Ser Thr Val Gln Leu Val Thr Gln Leu
785                 790                 795                 800
Met Pro Tyr Gly Cys Leu Leu Asp His Val Arg Glu Asn Arg Gly Arg
                805                 810                 815
Leu Gly Ser Gln Asp Leu Leu Asn Trp Cys Met Gln Ile Ala Lys Gly
            820                 825                 830
Met Ser Tyr Leu Glu Asp Val Arg Leu Val His Arg Asp Leu Ala Ala
        835                 840                 845
Arg Asn Val Leu Val Lys Ser Pro Asn His Val Lys Ile Thr Asp Phe
    850                 855                 860
Gly Leu Ala Arg Leu Leu Asp Ile Asp Glu Thr Glu Tyr His Ala Asp
865                 870                 875                 880
Gly Gly Lys Val Pro Ile Lys Trp Met Ala Leu Glu Ser Ile Leu Arg
                885                 890                 895
Arg Arg Phe Thr His Gln Ser Asp Val Trp Ser Tyr Gly Val Thr Val
            900                 905                 910
Trp Glu Leu Met Thr Phe Gly Ala Lys Pro Tyr Asp Gly Ile Pro Ala
        915                 920                 925
Arg Glu Ile Pro Asp Leu Leu Glu Lys Gly Glu Arg Leu Pro Gln Pro
    930                 935                 940
Pro Ile Cys Thr Ile Asp Val Tyr Met Ile Met Val Lys Cys Trp Met
945                 950                 955                 960
Ile Asp Ser Glu Cys Arg Pro Arg Phe Arg Glu Leu Val Ser Glu Phe
                965                 970                 975
Ser Arg Met Ala Arg Asp Pro Gln Arg Phe Val Val Ile Gln Asn Glu
            980                 985                 990
Asp Leu Gly Pro Ala Ser Pro Leu Asp Ser Thr Phe Tyr Arg Ser Leu
        995                 1000                1005
Leu Glu Asp Asp Asp Met Gly Asp Leu Val Asp Ala Glu Glu Tyr Leu
    1010                1015                1020
Val Pro Gln Gln Gly Phe Phe Cys Pro Asp Pro Ala Pro Gly Ala Gly
1025                1030                1035                1040
Gly Met Val His His Arg His Arg Ser Ser Ser Thr Arg Ser Gly Gly
                1045                1050                1055
Gly Asp Leu Thr Leu Gly Leu Glu Pro Ser Glu Glu Glu Ala Pro Arg
            1060                1065                1070
Ser Pro Leu Ala Pro Ser Glu Gly Ala Gly Ser Asp Val Phe Asp Gly
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Asp Leu Gly Met Gly Ala Ala Lys Gly Leu Gln Ser Leu Pro Thr His
    1090                1095                1100
Asp Pro Ser Pro Leu Gln Arg Tyr Ser Glu Asp Pro Thr Val Pro Leu
1105                1110                1115                1120
Pro Ser Glu Thr Asp Gly Tyr Val Ala Pro Leu Thr Cys Ser Pro Gln
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Pro Glu Tyr Val Asn Gln Pro Asp Val Arg Pro Gln Pro Pro Ser Pro
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            1140                1145                1150
Arg Glu Gly Pro Leu Pro Ala Ala Arg Pro Ala Gly Ala Thr Leu Glu
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Arg Ala Lys Thr Leu Ser Pro Gly Lys Asn Gly Val Val Lys Asp Val
    1170                1175                1180
Phe Ala Phe Gly Gly Ala Val Glu Asn Pro Glu Tyr Leu Thr Pro Gln
1185                1190                1195                1200
Gly Gly Ala Ala Pro Gln Pro His Pro Pro Pro Ala Phe Ser Pro Ala
                1205                1210                1215
Phe Asp Asn Leu Tyr Tyr Trp Asp Gln Asp Pro Pro Glu Arg Gly Ala
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Leu Gly Leu Asp Val Pro Val
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<210> 595
<211> 4530
<212> DNA
<213> Homo sapiens

<400> 595

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<210> 596
<211> 976
<212> PRT
<213> Homo sapiens

<400> 596
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Thr Phe Phe Lys Ser Phe Asn Lys Cys Thr Glu Asp Asp Leu Glu Phe
        35   40   45
Pro Phe Ala Lys Thr Asn Leu Ser Lys Asn Gly Glu Asn Ile Asp Ser
    50   55   60

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Asp Pro Ala Leu Gln Lys Val Asn Phe Leu Pro Val Leu Glu Gln Val
65                  70                  75                  80
Gly Asn Ser Asp Cys His Tyr Gln Glu Gly Leu Lys Asp Ser Asp Leu
                85                  90                  95
Glu Asn Ser Glu Gly Leu Ser Arg Val Phe Ser Lys Leu Tyr Lys Glu
            100                 105                 110
Ala Glu Lys Ile Lys Lys Trp Lys Val Ser Thr Glu Ala Glu Leu Arg
        115                 120                 125
Gln Lys Glu Ser Lys Leu Gln Glu Asn Arg Lys Ile Ile Glu Ala Gln
    130                 135                 140
Arg Lys Ala Ile Gln Glu Leu Gln Phe Gly Asn Glu Lys Val Ser Leu
145                 150                 155                 160
Lys Leu Glu Glu Gly Ile Gln Glu Asn Lys Asp Leu Ile Lys Glu Asn
                165                 170                 175
Asn Ala Thr Arg His Leu Cys Asn Leu Leu Lys Glu Thr Cys Ala Arg
            180                 185                 190
Ser Ala Glu Lys Thr Lys Lys Tyr Glu Tyr Glu Arg Glu Glu Thr Arg
        195                 200                 205
Gln Val Tyr Met Asp Leu Asn Asn Asn Ile Glu Lys Met Ile Thr Ala
    210                 215                 220
His Gly Glu Leu Arg Val Gln Ala Glu Asn Ser Arg Leu Glu Met His
225                 230                 235                 240
Phe Lys Leu Lys Glu Asp Tyr Glu Lys Ile Gln His Leu Glu Gln Glu
                245                 250                 255
Tyr Lys Lys Glu Ile Asn Asp Lys Glu Lys Gln Val Ser Leu Leu Leu
            260                 265                 270
Ile Gln Ile Thr Glu Lys Glu Asn Lys Met Lys Asp Leu Thr Phe Leu
        275                 280                 285
Leu Glu Glu Ser Arg Asp Lys Val Asn Gln Leu Glu Glu Lys Thr Lys
    290                 295                 300
Leu Gln Ser Glu Asn Leu Lys Gln Ser Ile Glu Lys Gln His His Leu
305                 310                 315                 320
Thr Lys Glu Leu Glu Asp Ile Lys Val Ser Leu Gln Arg Ser Val Ser
                325                 330                 335
Thr Gln Lys Ala Leu Glu Glu Asp Leu Gln Ile Ala Thr Lys Thr Ile
            340                 345                 350
Cys Gln Leu Thr Glu Glu Lys Glu Thr Gln Met Glu Glu Ser Asn Lys
        355                 360                 365
Ala Arg Ala Ala His Ser Phe Val Val Thr Glu Phe Glu Thr Thr Val
    370                 375                 380
Cys Ser Leu Glu Glu Leu Leu Arg Thr Glu Gln Gln Arg Leu Glu Lys
385                 390                 395                 400
Asn Glu Asp Gln Leu Lys Ile Leu Thr Met Glu Leu Gln Lys Lys Ser
                405                 410                 415
Ser Glu Leu Glu Glu Met Thr Lys Leu Thr Asn Asn Lys Glu Val Glu
            420                 425                 430
Leu Glu Glu Leu Lys Lys Val Leu Gly Glu Lys Glu Thr Leu Leu Tyr
        435                 440                 445
Glu Asn Lys Gln Phe Glu Lys Ile Ala Glu Glu Leu Lys Gly Thr Glu
    450                 455                 460
Gln Glu Leu Ile Gly Leu Leu Gln Ala Arg Glu Lys Glu Val His Asp
465                 470                 475                 480
Leu Glu Ile Gln Leu Thr Ala Ile Thr Thr Ser Glu Gln Tyr Tyr Ser
                485                 490                 495
Lys Glu Val Lys Asp Leu Lys Thr Glu Leu Glu Asn Glu Lys Leu Lys
            500                 505                 510
Asn Thr Glu Leu Thr Ser His Cys Asn Lys Leu Ser Leu Glu Asn Lys
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        515                 520                 525
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    530                 535                 540
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545                 550                 555                 560
Gln Ile Glu Asn Leu Gln Glu Thr Glu Thr Gln Leu Arg Asn Glu Leu
                565                 570                 575
Glu Tyr Val Arg Glu Glu Leu Lys Gln Lys Arg Asp Glu Val Lys Cys
            580                 585                 590
Lys Leu Asp Lys Ser Glu Glu Asn Cys Asn Asn Leu Arg Lys Gln Val
        595                 600                 605
Glu Asn Lys Asn Lys Tyr Ile Glu Glu Leu Gln Gln Glu Asn Lys Ala
    610                 615                 620
Leu Lys Lys Lys Gly Thr Ala Glu Ser Lys Gln Leu Asn Val Tyr Glu
625                 630                 635                 640
Ile Lys Val Asn Lys Leu Glu Leu Glu Leu Glu Ser Ala Lys Gln Lys
                645                 650                 655
Phe Gly Glu Ile Thr Asp Thr Tyr Gln Lys Glu Ile Glu Asp Lys Lys
            660                 665                 670
Ile Ser Glu Glu Asn Leu Leu Glu Glu Val Glu Lys Ala Lys Val Ile
        675                 680                 685
Ala Asp Glu Ala Val Lys Leu Gln Lys Glu Ile Asp Lys Arg Cys Gln
    690                 695                 700
His Lys Ile Ala Glu Met Val Ala Leu Met Glu Lys His Lys His Gln
705                 710                 715                 720
Tyr Asp Lys Ile Ile Glu Glu Arg Asp Ser Glu Leu Gly Leu Tyr Lys
                725                 730                 735
Ser Lys Glu Gln Glu Gln Ser Ser Leu Arg Ala Ser Leu Glu Ile Glu
            740                 745                 750
Leu Ser Asn Leu Lys Ala Glu Leu Leu Ser Val Lys Lys Gln Leu Glu
        755                 760                 765
Ile Glu Arg Glu Glu Lys Glu Lys Leu Lys Arg Glu Ala Lys Glu Asn
    770                 775                 780
Thr Ala Thr Leu Lys Glu Lys Lys Asp Lys Lys Thr Gln Thr Phe Leu
785                 790                 795                 800
Leu Glu Thr Pro Glu Ile Tyr Trp Lys Leu Asp Ser Lys Ala Val Pro
                805                 810                 815
Ser Gln Thr Val Ser Arg Asn Phe Thr Ser Val Asp His Gly Ile Ser
            820                 825                 830
Lys Asp Lys Arg Asp Tyr Leu Trp Thr Ser Ala Lys Asn Thr Leu Ser
        835                 840                 845
Thr Pro Leu Pro Lys Ala Tyr Thr Val Lys Thr Pro Thr Lys Pro Lys
    850                 855                 860
Leu Gln Gln Arg Glu Asn Leu Asn Ile Pro Ile Glu Glu Ser Lys Lys
865                 870                 875                 880
Lys Arg Lys Met Ala Phe Glu Phe Asp Ile Asn Ser Asp Ser Ser Glu
                885                 890                 895
Thr Thr Asp Leu Leu Ser Met Val Ser Glu Glu Glu Thr Leu Lys Thr
            900                 905                 910
Leu Tyr Arg Asn Asn Asn Pro Pro Ala Ser His Leu Cys Val Lys Thr
        915                 920                 925
Pro Lys Lys Ala Pro Ser Ser Leu Thr Thr Pro Gly Pro Thr Leu Lys
    930                 935                 940
Phe Gly Ala Ile Arg Lys Met Arg Glu Asp Arg Trp Ala Val Ile Ala
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Lys Met Asp Arg Lys Lys Lys Leu Lys Glu Ala Glu Lys Leu Phe Val
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<210> 597
<211> 3393
<212> DNA
<213> Homo sapiens

<400> 597
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<210> 598
<211> 188
<212> PRT
<213> Homo sapiens

<400> 598

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Ser Lys Lys Glu Trp Glu Lys Met Lys Ser Ser Glu Lys Ile Val Tyr
        35                  40                  45
Val Tyr Met Lys Leu Asn Tyr Glu Val Met Thr Lys Leu Gly Phe Lys
    50                  55                  60
Val Thr Leu Pro Pro Phe Met Arg Ser Lys Arg Ala Ala Asp Phe His
65                  70                  75                  80
Gly Asn Asp Phe Gly Asn Asp Arg Asn His Arg Asn Gln Val Glu Arg
                85                  90                  95
Pro Gln Met Thr Phe Gly Ser Leu Gln Arg Ile Phe Pro Lys Ile Met
            100                 105                 110
Pro Lys Lys Pro Ala Glu Glu Glu Asn Gly Leu Lys Glu Val Pro Glu
        115                 120                 125
Ala Ser Gly Pro Gln Asn Asp Gly Lys Gln Leu Cys Pro Pro Gly Asn
    130                 135                 140
Pro Ser Thr Leu Glu Lys Ile Asn Lys Thr Ser Gly Pro Lys Arg Gly
145                 150                 155                 160
Lys His Ala Trp Thr His Arg Leu Arg Glu Arg Lys Gln Leu Val Val
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Tyr Glu Glu Ile Ser Asp Pro Glu Glu Asp Asp Glu
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<210> 599
<211> 576
<212> DNA
<213> Homo sapiens

<400> 599

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<210> 600
<211> 262
<212> PRT
<213> Homo sapiens

<400> 600
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Gln His Ser Gln Pro Trp Gln Ala Ala Leu Tyr His Phe Ser Thr Phe
35 40 45
Gln Cys Gly Gly Ile Leu Val His Arg Gln Trp Val Leu Thr Ala Ala
50 55 60
His Cys Ile Ser Asp Asn Tyr Gln Leu Trp Leu Gly Arg His Asn Leu
65 70 75 80
Phe Asp Asp Glu Asn Thr Ala Gln Phe Val His Val Ser Glu Ser Phe
85 90 95
Pro His Pro Gly Phe Asn Met Ser Leu Leu Glu Asn His Thr Arg Gln
100 105 110
Ala Asp Glu Asp Tyr Ser His Asp Leu Met Leu Leu Arg Leu Thr Glu
115 120 125
Pro Ala Asp Thr Ile Thr Asp Ala Val Lys Val Val Glu Leu Pro Thr
130 135 140
Gln Glu Pro Glu Val Gly Ser Thr Cys Leu Ala Ser Gly Trp Gly Ser
145 150 155 160
Ile Glu Pro Glu Asn Phe Ser Phe Pro Asp Asp Leu Gln Cys Val Asp
165 170 175
Leu Lys Ile Leu Pro Asn Asp Glu Cys Glu Lys Ala His Val Gln Lys
180 185 190
Val Thr Asp Phe Met Leu Cys Val Gly His Leu Glu Gly Gly Lys Asp
195 200 205
Thr Cys Val Gly Asp Ser Gly Gly Pro Leu Met Cys Asp Gly Val Leu
210 215 220
Gln Gly Val Thr Ser Trp Gly Tyr Val Pro Cys Gly Thr Pro Asn Lys
225 230 235 240
Pro Ser Val Ala Val Arg Val Leu Ser Tyr Val Lys Trp Ile Glu Asp
245 250 255
Thr Ile Ala Glu Asn Ser
260

<210> 601
<211> 269
<212> PRT
<213> Homo sapiens

<400> 601
Met Ile Arg Thr Leu Leu Leu Ser Thr Leu Val Ala Gly Ala Leu Ser
1 5 10 15
Cys Gly Asp Pro Thr Tyr Pro Pro Tyr Val Thr Arg Val Val Gly Gly
20 25 30
Glu Glu Ala Arg Pro Asn Ser Trp Pro Trp Gln Val Ser Leu Gln Tyr
35 40 45
Ser Ser Asn Gly Lys Trp Tyr His Thr Cys Gly Gly Ser Leu Ile Ala
50 55 60

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Asn Ser Trp Val Leu Thr Ala Ala His Cys Ile Ser Ser Ser Arg Thr
65                  70                  75                  80
Tyr Arg Val Gly Leu Gly Arg His Asn Leu Tyr Val Ala Glu Ser Gly
                85                  90                  95
Ser Leu Ala Val Ser Val Ser Lys Ile Val Val His Lys Asp Trp Asn
            100                 105                 110
Ser Asn Gln Ile Ser Lys Gly Asn Asp Ile Ala Leu Leu Lys Leu Ala
        115                 120                 125
Asn Pro Val Ser Leu Thr Asp Lys Ile Gln Leu Ala Cys Leu Pro Pro
    130                 135                 140
Ala Gly Thr Ile Leu Pro Asn Asn Tyr Pro Cys Tyr Val Thr Gly Trp
145                 150                 155                 160
Gly Arg Leu Gln Thr Asn Gly Ala Val Pro Asp Val Leu Gln Gln Gly
                165                 170                 175
Arg Leu Leu Val Val Asp Tyr Ala Thr Cys Ser Ser Ser Ala Trp Trp
            180                 185                 190
Gly Ser Ser Val Lys Thr Ser Met Ile Cys Ala Gly Gly Asp Gly Val
        195                 200                 205
Ile Ser Ser Cys Asn Gly Asp Ser Gly Gly Pro Leu Asn Cys Gln Ala
    210                 215                 220
Ser Asp Gly Arg Trp Gln Val His Gly Ile Val Ser Phe Gly Ser Arg
225                 230                 235                 240
Leu Gly Cys Asn Tyr Tyr His Lys Pro Ser Val Phe Thr Arg Val Ser
                245                 250                 255
Asn Tyr Ile Asp Trp Ile Asn Ser Val Ile Ala Asn Asn
            260                 265
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<210> 602
<211> 269
<212> PRT
<213> Homo sapiens

<400> 602

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Met Ile Arg Thr Leu Leu Leu Ser Thr Leu Val Ala Gly Ala Leu Ser
 1               5                  10                  15
Cys Gly Val Ser Thr Tyr Ala Pro Asp Met Ser Arg Met Leu Gly Gly
            20                  25                  30
Glu Glu Ala Arg Pro Asn Ser Trp Pro Trp Gln Val Ser Leu Gln Tyr
        35                  40                  45
Ser Ser Asn Gly Gln Trp Tyr His Thr Cys Gly Gly Ser Leu Ile Ala
    50                  55                  60
Asn Ser Trp Val Leu Thr Ala Ala His Cys Ile Ser Ser Ser Arg Ile
65                  70                  75                  80
Tyr Arg Val Met Leu Gly Gln His Asn Leu Tyr Val Ala Glu Ser Gly
                85                  90                  95
Ser Leu Ala Val Ser Val Ser Lys Ile Val Val His Lys Asp Trp Asn
            100                 105                 110
Ser Asn Gln Val Ser Lys Gly Asn Asp Ile Ala Leu Leu Lys Leu Ala
        115                 120                 125
Asn Pro Val Ser Leu Thr Asp Lys Ile Gln Leu Ala Cys Leu Pro Pro
    130                 135                 140
Ala Gly Thr Ile Leu Pro Asn Asn Tyr Pro Cys Tyr Val Thr Gly Trp
145                 150                 155                 160
Gly Arg Leu Gln Thr Asn Gly Ala Leu Pro Asp Asp Leu Lys Gln Gly
                165                 170                 175
Arg Leu Leu Val Val Asp Tyr Ala Thr Cys Ser Ser Ser Gly Trp Trp
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            180                 185                 190
Gly Ser Thr Val Lys Thr Asn Met Ile Cys Ala Gly Gly Asp Gly Val
        195                 200                 205
Ile Cys Thr Cys Asn Gly Asp Ser Gly Gly Pro Leu Asn Cys Gln Ala
    210                 215                 220
Ser Asp Gly Arg Trp Glu Val His Gly Ile Gly Ser Leu Thr Ser Val
225                 230                 235                 240
Leu Gly Cys Asn Tyr Tyr Tyr Lys Pro Ser Ile Phe Thr Arg Val Ser
                245                 250                 255
Asn Tyr Asn Asp Trp Ile Asn Ser Val Ile Ala Asn Asn
            260                 265
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